RESEARCH ARTICLE

Perioperative Antibiotics to Prevent Acute Endophthalmitis after Ophthalmic Surgery: A Systematic Review and Meta-Analysis

Jin Zhu Huang¹, Xiaofang Wang², Xiaohong Chen³, Qiuyue Song⁴, Wen Liu¹, Laichun Lu⁵*

¹ Department of Pharmacy, Daping Hospital, Third Military Medical University, Chongqing, China, ² Department of Laboratory Medicine, Key Laboratory of Diagnostic Medicine (Ministry of Education), Chongqing Medical University, Chongqing, China, ³ Department of Pharmacy, Chongqing Health Center for Women and Children, Chongqing, China, ⁴ Department of Health Statistics, Third Military Medical University, Chongqing, China, ⁵ College of Pharmacy, Third Military Medical University, Chongqing, China

* lulab2014@126.com

Abstract

Background

Post-operative endophthalmitis is a rare and dreaded complication in ophthalmic operations because it often induces irreparable vision loss. Although many ophthalmological studies aimed at reducing the rate of endophthalmitis have been performed around the world, controversy continues to surround some issues, including the choice of antimicrobials and their route of administration, duration and timing. The aim of this study is to investigate some of these unresolved issues.

Methods

A systematic review and meta-analysis of randomized controlled trials and observational studies was performed. The PubMed, EMBASE, Cochrane Library and Clinical Trials databases were searched to identify studies published until Feb. 2016. The relative risk (RR) for each clinical outcome data is presented with 95% confidence intervals (CIs). Pooled estimates of effects were calculated using random-effect models.

Results

Thirty-four studies from twenty-four reports involving 1264797 eyes were included in this analysis. Endophthalmitis occurred, on average, in one out of 6177 eyes when intracameral vancomycin/moxifloxacin were used and in one out of 1517 eyes when intracameral vancomycin/moxifloxacin were not used. The relative risk (95% CI) of endophthalmitis was reduced to 0.20 (0.10, 0.42) when intracameral antibiotics were used (p < 0.0001). The subconjunctival injection of antibiotics was not superior to other administration routes included in this study (RR = 1.67, 95% CI (0.55, 5.05), p = 0.36). A statistically significant difference was found in the rate of endophthalmitis between the use and lack of use of topical antibiotics (RR = 0.65, 95% CI (0.43, 0.99), p = 0.04). However, no statistically significant
difference was found in microbial isolation rates between these groups (RR = 0.77, 95% CI (0.34, 1.75), p = 0.53). When long-term and short-term use of topical antibiotics before surgery were compared, a statistically significant difference was found in microbial isolation rates (RR = 0.57, 95% CI (0.44, 0.74), p<0.0001).

Conclusions
This meta-analysis concluded intracameral antibiotics are effective at preventing endophthalmitis in ocular surgery. A randomized controlled trial confirms the efficacy of cefuroxime but recent large cohort studies support the efficacy of vancomycin/moxifloxacin intracamerally. Intracameral antibiotics are superior to subconjunctival injections but that irrigation antibiotic data are not of enough quality to make a comparison. Different results were found in two clinical outcomes between the use or lack of use of topical antibiotic therapy, we did not find sufficient evidence to conclude that its use prevents endophthalmitis.

Introduction
Post-operative endophthalmitis is a complication that can follow all ophthalmic procedures. Endophthalmitis is a calamitous event that can result in a patient suffering the loss of sight. Since 2000, the reported frequency of endophthalmitis is low worldwide, ranging from 0% to 0.63% [1]. Coagulase-negative *Staphylococcus* species are the organisms that are most frequently isolated from patients who develop postoperative endophthalmitis after cataract surgery. It is followed by coagulase-positive *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, and *Corynebacterium* species [2–7]. In pars plana vitrectomies, the reported bacteria include coagulase-negative *Staphylococcus* species, *Pseudomonas* species, *Propionibacterium* species, *Enterococcus* species, and *Bacillus* species [8]. Preoperative, intraoperative, and postoperative risk factors have been reported by some ophthalmologists. Diabetes mellitus, an immunocompromised state, chronic blepharitis, lacrimal passage infection, contaminated eyedrops, contact lens use, contralateral prosthesis and gender are preoperative factors, while the application of 2% xylocaine gel before povidone-iodine instillation, prolonged surgery, secondary surgery, posterior capsular rupture, vitreous loss and contaminated irrigating solution are intraoperative factors. Wound leakage, vitreous incarceration and behaviors (e.g., eye rubbing and personal hygiene) are associated with the development of post-operative endophthalmitis [9]. To reduce its incidence, many measures have been employed by ophthalmologists around the world. These include the use of topical antibiotics, intracameral antibiotics, subconjunctival antibiotic injections, lash trimming, saline irrigation, and antibiotic-containing irrigating solutions. However, the most frequent measure is the use of povidone-iodine before surgery to decrease contamination by ocular microbes and prevent postoperative endophthalmitis [10–12]. Not all of these techniques have been found to influence clinical outcomes. Intracameral cephalosporin (cefazolin, cefuroxime) has been shown to be effective in randomized controlled trials and meta-analyses [13–14]. An increasing number of ophthalmologists have supported the use of intracameral cefuroxime to prevent postoperative endophthalmitis because of the ECRS study. However, as a result of the severe drug resistance of the causal bacteria, some new intracameral antibiotics, such as vancomycin and moxifloxacin, have been suggested to avoid endophthalmitis [15–21]. The subconjunctival injection and topical application of antibiotics have also been used by some ophthalmology centers, but the results of different reports have varied. This paper focuses on the use of intracameral
vancomycin/moxifloxacin and the subconjunctival injection and topical application of antibiotics. The timing of topical drops was also analyzed. We sought to use a systemic review and meta-analysis to discuss those controversial issues.

**Materials and Methods**

**Search Strategy**

A comprehensive literature search was performed to identify studies published until Feb. 2016. The PubMed, EMBASE, Cochrane Library, and Clinical Trials databases were the main sources that were searched. Other routes (e.g., hand-search and library resource sharing) were also considered. Ophthalmologic surgical procedures, cataract extractions, vitrectomies, keratoplasties, intraocular lens implantations, glaucoma procedures, strabotomies, retinal detachment repair, laser in situ keratomileusis, laser-assisted subepithelial keratectomy, antimicrobial, antibacterial agents, antibiotic prophylaxis, anti-infective agent and eye surgery were the search terms that were used. The specific searching strategy is described in S1 Table.

**Inclusion and Exclusion Criteria**

Studies were included if they met the following criteria: (i) random studies and observational studies, (ii) compared endophthalmitis rates or microbial isolation rates in two comparable populations, (iii) received/did not receive intracameral vancomycin/moxifloxacin therapy, or received/did not receive subconjunctival antibiotic injection, or received/did not receive topical antibiotics or compared administration with different timing, (iv) published from January 2000-February 2016 (reduced the influence of new operations), and (v) exceeded 1000 individuals if the study reported endophthalmitis rates and 50 if it reported microbial isolation rates. Studies were excluded if they: (i) were not written in English, (ii) were incomplete or included duplicated data, (iii) did not contain any predetermined clinical outcomes, (iv) could not be pooled with other included studies, (v) did not instill topical antibiotics (in terms of the group received topical antibiotics), and (vi) had no conformity at baseline with other studies in the timing (antibiotic drops and povidone–iodine were administered before surgery) and site of the analyzed specimen (conjunctival sac).

**Data extraction**

The data were extracted independently by two authors (JZH and XHC). A standardized form was designed before the extraction to collect information including first author, publication date, mean age, male (%), type of surgery, study design, follow-up time, no. of eyes, therapeutic regimen, timing and clinical outcomes. If disagreements arose between these two authors, all final decisions were made by LCL and QYS after a discussion.

**Quality assessment**

Randomized controlled trials (RCT) and observational studies were included in our analysis, and the quality assessment of those data is described in the S1 File. Observational studies were evaluated using the Newcastle–Ottawa scale (NOS) [22]. Nine items comprised the check list, and every item accounted for 1 point in each of three parts (selection, comparability and exposure). If a score was larger than 6, the study was determined to be of high quality. RCTs were assessed using the recommendations of the Cochrane Collaboration [23].
Outcomes analyzed

In the current data set, the rate of endophthalmitis was the best and most direct clinical outcome that could be used to measure the effect of prophylactic antimicrobial agents. However, because postoperative endophthalmitis is rare, some studies also selected the microbial isolation rate as their outcome. In the analysis in this study, the rate of endophthalmitis was used as the primary outcome, and the microbial isolation rate was the secondary outcome.

Statistical analysis

In this meta-analysis, we used risk ratios (RR) with 95% confidence intervals (CIs) to present dichotomous outcomes or enumeration data and random-effect models to calculate pooled estimates of effects. In light of fact that the rate of endophthalmitis was low, in case-control studies, the odds ratio (OR) was considered to be approximately equal to the RR. The I² statistic was used to assess heterogeneity among studies. We considered the I² values from 0% to 24%, 25% to 50% and greater than 50% to indicate low, moderate and high heterogeneity, respectively [23]. To decrease heterogeneity and increase reliability, a subgroup analysis was performed for every comparable group. Forest plots, the risk of bias in randomized controlled trials and the above-mentioned traits were analyzed using RevMan version 5.1. Furthermore, the analyses to determine sensitivity and publication bias analysis using Stata version 12.0.

Results

Results of the search and study characteristics

Up to February 2016, a total of 688 reports were identified through database searches, and 34 studies included in 24 reports involving 1264797 eyes were included in the final analysis [2, 13, 15–21, 24–38]. The detailed screening process is described in Fig 1. Of the remaining reports, there were nine RCTs [13, 30–37] and fourteen observational studies [2, 15–21, 24, 27–29, 38]. A total of 21 studies reported the rate of postoperative endophthalmitis [2, 13, 15–21, 24, 27–29, 38], and 13 studies reported the microbial isolation rate [25, 26, 30–37]. Thirty studies [2, 13, 15–21, 24, 27–30, 33–37, 38] included only eyes that received cataract surgery, but an additional four studies [25–26, 31–32] included other intraocular surgeries. The characteristics of the included studies are shown in Table 1.

The Rate of Postoperative Endophthalmitis

**Intracameral Antibiotic.** Nine studies compared patients who received/did not receive intracameral vancomycin/moxifloxacin therapy [15–21, 38]. A significant difference was found in the meta-analysis results, which suggested that the rate of postoperative endophthalmitis was lower in the intracameral vancomycin/moxifloxacin group (OR = 0.20, 95% CI (0.10, 0.42), p < 0.0001, I² = 45%) (Fig 2A). In the subgroup analysis, the results in the moxifloxacin group was homologous (OR = 0.21, 95%CI (0.12, 0.37), p < 0.00001, I² = 0%) (Fig 2A). However, there was heterogeneity in the vancomycin group (OR = 0.11, 95%CI (0.01, 1.55), p = 0.10, I² = 81%) (Fig 2A).

**Subconjunctival antibiotic injections.** Seven studies reported the use of subconjunctival antibiotic injections [2, 24, 27–29]. When patients who received subconjunctival antibiotic injections were compared to those who did not, no significant difference was found (OR = 1.67, 95% CI (0.55, 5.05), p = 0.36, I² = 85%) (Fig 2B). Because I² = 85%, three subgroup analyses were performed to increase reliability. The results suggested that a significant difference was found between the subconjunctival antibiotic injections group and the intracameral
antibiotic and irrigation groups (intracameral antibiotic: OR = 3.76, 95% CI (1.92, 7.37), p = 0.0001, I² = 0%; irrigation: OR = 10.07, 95% CI (3.09, 32.88), p = 0.0001) (Fig 2B). When the subconjunctival antibiotic injection group was compared to the topical or PVI (povidone-iodine) group, there was no significant difference (OR = 0.43, 95% CI (0.15, 1.20), p = 0.11, I² = 68%) (Fig 2B).

**Topical Antibiotic.** The meta-analysis results revealed that there was a significant difference among the five studies (2, 13, 20, 24) that reported the rate of postoperative endophthalmitis (OR = 0.65, 95% CI (0.43, 0.99), p = 0.04, I² = 0%) (Fig 2C). However, when subgroups were analyzed, no significant difference was found except for in a retrospective study (OR = 0.49, 95% CI (0.26, 0.89), p = 0.02) (Fig 2C).
Table 1. Main characteristics of the studies included in the meta-analysis.

| First Author, Date | Age (%) | Type of Surgery | Study Design | Follow-up Time | No. of Eyes | T-therapeutic Regimen | Timing | Clinical Outcomes | Tde Quality of tde Study |
|--------------------|---------|-----------------|--------------|---------------|-------------|----------------------|--------|------------------|-------------------------|
| **Intracameral Antibiotic VS No Intracameral** | | | | | | | | | |
| Rush,2015           | 71.0    | CAS             | COS          | 3 months      | 9386        | 11333                | IC vancomycin, PVI | PVI PE PE RPE        | High                    |
| Anjeet,2010         | NA NA   | CAS             | COS          | 6 weeks       | 12702       | 3904                 | IC vancomycin, PVI | PVI PE PE RPE        | Moderate                |
| Rudnisky,2014       | NA NA   | CAS             | CCS          | 6 weeks       | 11818       | 59739                | IC vancomycin      | No intracameral antibiotic PE PE RPE Moderate |
| Rudnisky,2014       | NA NA   | CAS             | CCS          | 6 weeks       | 3738        | 59739                | IC moxifloxacin    | No intracameral antibiotic PE PE RPE Moderate |
| Shorstein,2013      | 74.0    | NA NA           | CAS          | 12 months     | 1890        | 3655                 | IC moxifloxacin, PVI | PVI PE PE RPE        | Moderate                |
| Haripriya,2016      | NA NA   | CAS             | COS          | 6 weeks       | 38160       | 78554                | IC moxifloxacin, PVI | PVI PE PE RPE        | High                    |
| Matsuura,2013       | NA NA   | CAS             | COS          | 1 month       | 18794       | 15958                | IC moxifloxacin, PVI | PVI PE PE RPE        | Moderate                |
| Friling,2013a       | NA 38.3 | CAS             | COS          | 10 months     | 6897        | 2804                 | IC moxifloxacin, PVI | PVI PE PE RPE        | High                    |
| Galvis,2014         | 67.2    | NA NA           | CAS          | 2 weeks       | 1618        | 1056                 | IC moxifloxacin, PVI | PVI PE PE RPE        | Moderate                |
| **Subconjunctival Injection Antibiotic VS No Subconjunctival Injection** | | | | | | | | | |
| Jabbarvand,2016b     | 79.0    | NA NA           | CAS          | 6 weeks       | 69120       | 25290                | SI antibiotic +PVI | IC+PVI PE PE RPE     | Moderate                |
| Jabbarvand,2016c     | 79.0    | NA NA           | CAS          | 6 weeks       | 69120       | 76800                | SI antibiotic +PVI | topica l antibiotic +PVI PE PE RPE Moderate |
| Jabbarvand,2016d     | 79.0    | NA NA           | CAS          | 6 weeks       | 69120       | 260744               | SI antibiotic +PVI | PVI PE PE RPE        | Moderate                |
| Asencio,2015         | 71.5    | NA NA           | CAS          | 6 weeks       | 5068        | 9217                 | SI gentamicin +PVI | Irrigation BBS + vancomycin + gentamicin +PVI PE PE RPE High |
| Tan,2012             | NA NA   | CAS             | COS          | 1 month      | 29539       | 20638                | SI gentamicin +PVI | Cefazolin +PVI      | PE PE RPE Moderate     |
| Yu-Wai,2008          | NA NA   | CAS             | COS          | 3 weeks      | 19425       | 17318                | SI cefoxime +PVI   | Cefasol +PVI         | PE PE RPE Moderate     |
| Colleaux,2000b       | NA NA   | CAS             | COS          | NA           | 8856        | 5030                 | SI gentamicin + cefazolin +PVI | PVI +Topical antibiotic PE PE RPE Moderate |
| **Topical Antibiotic VS No Topical Antibiotic** | | | | | | | | | |
| ESCR S,2007a         | NA NA   | CAS             | RCT          | 6 weeks       | 4000        | 3997                 | Topical moxifloxacin +IC cefoxime +PVI | Placebo +IC cefoxime +PVI PE PE RPE High |
| ESCR S,2007b         | NA NA   | CAS             | RCT          | 6 weeks       | 3984        | 3990                 | Topical moxifloxacin +PVI | Placebo +PVI PE PE RPE High |
| Coskun,2011a         | 51.2    | CAS             | RCT          | NA           | 54          | 53                   | Topical ciprofloxac in | Placebo +PVI PE PE MIR Moderate |
| Coskun,2011b         | 51.2    | CAS             | RCT          | NA           | 57          | 53                   | Topical ofloxacin  | Placebo +PVI PE PE MIR Moderate |
| Eyal,2009            | 69.7    | OCS             | RCT          | 72 hours     | 237         | 227                  | Topical moxifloxacin +PVI | Placebo +PVI PE PE MIR Moderate |

(Continued)
Microbial Isolation Rate

**Topical Antibiotic.** There were four studies [30–32] that provided a microbial isolation rate, and the results of these studies suggested that there was no significant difference (OR = 0.77, 95% CI (0.34, 1.75), p = 0.53, I² = 72%) (Fig 3A). A subgroup analysis was performed, but the results were similar (only topical antibiotic: OR = 0.74, 95% CI (0.17, 3.27), p = 0.69, I² = 83%; topical antibiotic + PVI: OR = 0.77, 95% CI (0.19, 3.09), p = 0.71, I² = 77%) (Fig 3A).

**Timing.** When long-term and short-term use of a topical antibiotic before ocular surgery was analyzed, nine studies that had consistent baselines were included (25–26, 33–37). The meta-analysis revealed that short-term use was associated with an increased incidence of

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**Table 1. (Continued)**

| First Author , Date | Age (Mean) | Male (%) | Type of Surgery | Study Design | Follow-up Time | No. of Eyes | Therapeutic Regimen | Timing | Clinical Outcomes | The Quality of the Study |
|---------------------|------------|----------|-----------------|--------------|---------------|-------------|---------------------|--------|-------------------|--------------------------|
| Kaspar,2008         | 67.8       | 34.1     | OCS             | RCT          | 10 days       | 67          | 65                  | T      | PVI               | PE PE MIR High           |
| Colleaux,2000a      | NA         | NA       | CAS             | COS          | NA 12152 1734 | Topical Tobramycin or Gentamicin or Ofloxacin or Polymyxin-trimethoprim | SI antibiotic +PVI | PE PE RPE Moderate |
| Frilling,2013b      | NA         | NA       | CAS             | COS          | 10 months 7307 396894 | Topical chloramphenicol or fusidic acid | IC antibiotic +PVI | PE PE RPE High |
| Jabbarvand,2016a    | 79.0       | NA       | CAS             | RCS          | 6 weeks 76800 260744 | Topical ciprofloxacin +PVI | PVI PE PE RPE Moderate |

**Long time VS Short Time of Topical Antibiotic**

| Bing,2015           | 70.6       | 50.4     | CAS             | RCT          | 5 days       | 69          | 64                  | 1d 1h MIR Moderate |
| Inoue,2008a         | 74.0       | 46.3     | CAS             | RCT          | 5 days       | 79          | 76                  | Topical levofloxacin | Topical levofloxacin 3d 1h MIR Moderate |
| Inoue,2008b         | 74.0       | 46.3     | CAS             | RCT          | 5 days       | 79          | 89                  | Topical levofloxacin | Topical levofloxacin 3d 1d MIR Moderate |
| Inoue,2008c         | 74.0       | 46.3     | CAS             | RCT          | 5 days       | 89          | 76                  | Topical levofloxacin | Topical levofloxacin 1d 1h MIR Moderate |
| Lingmin,2009        | 71.1       | 50.8     | OCS             | RCT          | 10 days      | 57          | 63                  | Topical moxifloxacin | Topical moxifloxacin 3d 1h MIR Moderate |
| Ta,2002             | NA         | NA       | CAS             | RCT          | 10 days      | 43          | 48                  | Topical ofloxacin 3d 1h MIR High  |
| Ta,2007             | NA         | NA       | CAS             | RCT          | 6 days       | 50          | 50                  | Topical levofloxacin 3d 1d MIR High  |
| Christopher,2008    | 69.3       | 68.3     | OCS             | COS          | 5 days       | 60          | 60                  | Topical moxifloxacin 1d 1h MIR Moderate |
| Jason,2008          | 67.7       | 58.3     | OCS             | COS          | 5 days       | 60          | 60                  | Topical gatifloxacin 1d 1h MIR Moderate |

**Footnotes:** Age: Mean age or median age. Abbreviations: NA = not available, T = treatment group, C = control group, CAS = cataract surgery, OCS = ocular surgery, COS = cohort study, CCS = case-control study, RCT = randomized controlled trial, RCS = retrospective cross-section study, IC = intracameral, SI = subconjunctival injection, PVI = povidone-iodine, PE = perioperation, 1d = 1 day before surgery, 3d = 3 days before surgery, 1h = within 1 hour before surgery, RPE = rate of postoperative endophthalmitis, MIR = microbial isolation rate.

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### Intracameral vs. Not Intracameral Events

| Study or Subgroup | Intracameral Events | Not Intracameral Events | Total Weights | Risk Ratio M-H Random 95% CI | Risk Ratio M-H Random 95% CI |
|-------------------|---------------------|-------------------------|--------------|----------------------------|----------------------------|
| **Outcomes**      | Total               | Total                   |              |                            |                            |
| **Intracameral**  |                     |                         |              |                            |                            |
| Arkipov, 2010     | 1287                 | 1508                    | 28,064       | 0.62 (0.30, 1.31)          |                            |
| Ruhlin, 2014      | 3                    | 96,732                  | 18,370       | 0.68 (0.34, 1.34)          |                            |
| Rush, 2014        | 2                    | 60,930                  | 4,571        | 0.65 (0.50, 0.89)          |                            |
| **Subtotal (95% CI)** | **35,700**           |                         |              |                            |                            |
| **Total events**  | **166**              |                         |              |                            |                            |
| **Heterogeneity: Tau^2 = 6.45; CI = 2.48, 10.48** | **P = 0.0001**          |                            |                            |                            |
| **Test for overall effect: Z = 2.87 (P = 0.004)** |                            |                            |                            |                            |

### Subconjunctival Antibiotic vs. Intracameral Antibiotic

| Subconjunctival Antibiotic | Intracameral Events | Not Intracameral Events | Total Weights | Risk Ratio M-H Random 95% CI | Risk Ratio M-H Random 95% CI |
|-----------------------------|---------------------|-------------------------|--------------|----------------------------|----------------------------|
| Jakobsson, 2010             | 9                    | 60,930                  | 18,370       | 0.68 (0.34, 1.34)          |                            |
| Tar, 2013                   | 13                   | 20,308                  | 4,571        | 0.65 (0.50, 0.89)          |                            |
| Yau, 2008                   | 27                   | 4,1710                  | 38,390       | 0.74 (0.37, 1.37)          |                            |
| **Subtotal (95% CI)**       | **56**               |                         |              |                            |                            |
| **Total events**            | **66**               |                         |              |                            |                            |
| **Heterogeneity: Tau^2 = 6.45; CI = 2.48, 10.48** | **P = 0.0001**          |                            |                            |                            |
| **Test for overall effect: Z = 2.87 (P = 0.004)** |                            |                            |                            |                            |

### Other Administration routes of antibiotic at the same time, non-RCT

| Study or Subgroup | Topical Events | Not Topical Events | Total Weights | Risk Ratio M-H Random 95% CI | Risk Ratio M-H Random 95% CI |
|-------------------|---------------|-------------------|--------------|----------------------------|----------------------------|
| **Outcomes**      | **Total**     | **Total**         |              |                            |                            |
| **Topical**       | **Total**     | **Total**         |              |                            |                            |
| **ESCOR/2007a**   | **4000**      | **4000**          |              |                            |                            |
| **Subtotal (95% CI)** | **4000**      | **4000**          |              |                            |                            |
| **Total events**  | **4000**      | **4000**          |              |                            |                            |
| **Heterogeneity: Not applicable** | **P = 0.66**              |                            |                            |                            |
| **Test for overall effect: Z = 0.45 (P = 0.66)** |                            |                            |                            |                            |

### Only Topical, RCT

| Study or Subgroup | Topical Events | Not Topical Events | Total Weights | Risk Ratio M-H Random 95% CI | Risk Ratio M-H Random 95% CI |
|-------------------|---------------|-------------------|--------------|----------------------------|----------------------------|
| **Outcomes**      | **Total**     | **Total**         |              |                            |                            |
| **ESCOR/2007b**   | **3984**      | **3984**          |              |                            |                            |
| **Subtotal (95% CI)** | **3984**      | **3984**          |              |                            |                            |
| **Total events**  | **3984**      | **3984**          |              |                            |                            |
| **Heterogeneity: Not applicable** | **P = 0.42**              |                            |                            |                            |
| **Test for overall effect: Z = 0.43 (P = 0.63)** |                            |                            |                            |                            |

### Only Topical, non-RCT

| Study or Subgroup | Topical Events | Not Topical Events | Total Weights | Risk Ratio M-H Random 95% CI | Risk Ratio M-H Random 95% CI |
|-------------------|---------------|-------------------|--------------|----------------------------|----------------------------|
| **Outcomes**      | **Total**     | **Total**         |              |                            |                            |
| **Johansson, 2016a** | **76800**    | **76800**         |              |                            |                            |
| **Subtotal (95% CI)** | **76800**    | **76800**         |              |                            |                            |
| **Total events**  | **76800**    | **76800**         |              |                            |                            |
| **Heterogeneity: Not applicable** | **P = 0.63**              |                            |                            |                            |
| **Test for overall effect: Z = 0.43 (P = 0.63)** |                            |                            |                            |                            |
microbial isolation (OR = 0.57, 95% CI (0.44, 0.74), p < 0.0001, I² = 40%) (Fig 3B). Because there was moderate heterogeneity (I² = 40%), a subgroup analysis was performed. A significance difference was found in the group that included two RCTs and that compared application between three days and within one hour before surgery (OR = 0.40, 95% CI (0.26, 0.63), p < 0.0001, I² = 0%) (Fig 3B). A significance difference was also found in the group that included two non-RCTs and that compared results between groups that were administered at one day and within one hour before surgery (OR = 0.56, 95% CI (0.39, 0.80), p = 0.002, I² = 0%) (Fig 3B). There was no difference between the other two subgroups (3 days VS 1 day, RCT: OR = 0.57, 95% CI (0.32, 1.02), p = 0.06, I² = 41%; 3 days VS 1 day, RCT: OR = 0.76, 95% CI (0.44, 1.32), p = 0.36, I² = 49%) (Fig 3B).

Publication Bias and Sensitivity Analysis

There was no significant publication bias according to the Begg’s and Egger’s funnel plot asymmetry tests that were performed in the meta-analysis (S2 File). The results of the sensitivity analysis were diverse, and the details are described in S3 File. In the group comparison between using and not using intracameral antibiotics, sensitivity was not influenced by the studies that were omitted obviously. The sensitivity analysis for receiving or not receiving subconjunctival antibiotic injections demonstrated that three studies (Colleaux,2000b, Jabbarvand,2016c and Jabbarvand,2016d) influenced the pooled effect size, and these studies were therefore deleted. New results that were similar to those of the subgroup analysis revealed that intracameral and irrigation antibiotics were superior to subconjunctival injections. In the case of topical antibiotics, we excluded the study (Jabbarvand, 2016a) because it influenced the sensitivity in the group that used RPE as a clinical outcome. When we then reanalyzed the data, we found that there was no statistical difference. Hence, that study should be deleted to increase the conclusion’s reliability. In the group in which MIR was used as the outcome, we re-conducted a subgroup analysis according to classifications of quinolone, but the result was similar to the previous result. The sensitivity analysis for the timing of application of topical antibiotics demonstrated that the study (Inoue, 2008c) exhibited slightly more influence on the pooled effect size than other studies, and this study was therefore deleted. The new result was almost the same as the initial result, but the heterogeneity was smaller. Because of the variety of available antibiotics, we also reanalyzed new subgroups according to the classifications of the drugs that were used. The result was similar to the previous result, but the heterogeneity was larger.

Discussion

The low rate of postoperative endophthalmitis makes it difficult to conduct a large RCT to investigate the optimal method for preventing it [39]. Based on the currently available clinical evidence, preoperative preparation with 5% povidone-iodine solution has consensus approval among ophthalmologists. However, no consensus has been reached regarding the agent of choice, the administration route or the timing of antimicrobial prophylaxis, and no agent has been FDA-approved for this indication in ophthalmic procedures [1]. For these reasons, we performed this meta-analysis. However, because of the absence of relevant RCTs, we also
Fig 3. Forest plot of the Microbial Isolation Rate (A: the effect of using VS not using Topical Antibiotics; B: the effect of Long-term VS Short-term use). The vertical line indicates no difference between the groups. RRs are represented by diamond shapes, and 95% CIs 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.

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included observational studies to resolve the problem mentioned above in this analysis. Since the ESCRS study, intracameral antibiotics have gradually gained acceptance around the world. Of those antibiotics, cefuroxime has been shown to be effective at reducing the rate of postoperative endophthalmitis. However, with the increase in resistant microorganisms, moxifloxacin and vancomycin have received an increasing amount of attention. The results of this meta-analysis show that intracameral moxifloxacin/vancomycin can prevent endophthalmitis. Unfortunately, no RCTs were included to address this point. Additionally, no study compared the use of cephalosporin with moxifloxacin or vancomycin. In addition to intracameral moxifloxacin/vancomycin, we also compared the results of administering subconjunctival antibiotic injections via other routes. According to our analysis, intracameral antibiotics were superior to subconjunctival injections, but subconjunctival injections were not superior to topical antibiotics or PVI. There is only one case-control study to compare irrigation antibiotics with subconjunctival injections, so the data is not enough quality to make a comparison. According to the results of this meta-analysis, we do not recommend subconjunctival antibiotic injections as a routine method for preventing endophthalmitis. Interestingly, when the timing of administration was not considered, topical antibiotics seemed to lose their value. The results were the same whether RPE or MIR was used as the clinical outcome. But there was a higher incidence of microbial isolation in short-term use than long-term use patients. The reason for this contradictory result might be that the efficiency of bacterial eradication varied with differences in the timing of topical antibiotics use. However, reducing the number of bacteria on the ocular surface is not the same as preventing endophthalmitis. Additionally, many topical antibiotics are used in combination, which makes it difficult to determine optimal timing [1]. The timing reported in the papers ranged from one hour to three days before the surgery [4, 11, 40–41]. Further investigations should be performed to optimize the best regimens. Given the results we obtained in the meta-analysis and the results from the ESCRS study, the use of topical antibiotics was not recommended. There are several limitations to our meta-analysis. First, few RCTs were included. Second, although we performed subgroup and sensitivity analyses, the I2 values remained large, especially in the topical antibiotic group, demonstrating that heterogeneity was high. The fact that we did not identify the reason for the heterogeneity may make the results unreliable. Third, some results were obtained from small sample studies. In addition, difficulties in diagnosing and defining endophthalmitis could also influence the primary data. For the studies that selected MIR as the clinical outcome, the method and duration of specimen cultivation might have made the results in the primary studies more diverse, which could have influenced our results. In conclusion, intracameral vancomycin/moxifloxacin therapy is effective for preventing postoperative endophthalmitis. Intracameral antibiotics are superior to subconjunctival injections, but that irrigation antibiotic data are not of enough quality to make a conclusion. Different results were found for topical antibiotic therapies between two clinical outcomes, and we did not find sufficient evidence to conclude that this technique prevents endophthalmitis. Long-term use of topical antibiotics before surgery appears to be more effective, but clearance the number of pathogens on the ocular surface is not the same as preventing endophthalmitis. So, topical antibiotics before surgery to prevent endophthalmitis were not recommended by this meta-analysis.

Supporting Information
S1 PRISMA Checklist. PRISMA Checklist for the meta-analysis.
(DOC)
S1 File. Quality assessment of included studies.
(DOCX)
Author Contributions

Conceptualization: JZH LCL.
Data curation: XHC XFW.
Formal analysis: JZH QYS.
Investigation: JZH XHC.
Methodology: JZH QYS XHC.
Project administration: JZH.
Resources: WL.
Software: QYS.
Supervision: LCL.
Validation: XHC.
Visualization: WL.
Writing – original draft: JZH XFW.
Writing – review & editing: LCL XFW.

References

1.  Am J Health Syst Pharm. Clinical practice guidelines for antimicrobial prophylaxis in surgery. 2013; 70 (3):195–283.
2.  Colleaux KM, Hamilton WK. Effect of prophylactic antibiotics and incision type on the incidence of endophthalmitis after cataract surgery. Can J Ophthalmol. 2000; 35: 373–378. doi: 10.1016/S0008-4122(00)80124-6 PMID: 11192445
3.  Garat M, Moser CL, Martin-Baranera M, Alonso-Tarrés C, Alvarez-Rubio L. Prophylactic intracameral cefazolin after cataract surgery: endophthalmitis risk reduction and safety results in a 6-year study. J Cataract Refract Surg. 2009; 35: 637–642. doi: 10.1016/j.jcrs.2008.12.023 PMID: 19304083
4.  Jensen MK, Fiscella RG, Moshirfar M, Mooney B. Third- and fourth-generation fluoroquinolones: retrospective comparison of endophthalmitis after cataract surgery performed over 10 years. J Cataract Refract Surg. 2008; 34: 1460–1467. doi: 10.1016/j.jcrs.2008.05.045 PMID: 18721704
5.  Moshirfar M, Feiz V, Vitale AT, Wegelin JA, Basavanthappa S, Wolsey DH. Endophthalmitis after uncomplicated cataract surgery with the use of fourth-generation fluoroquinolones: a retrospective observational case series. Ophthalmology. 2007; 114: 686–691. doi: 10.1016/j.ophtha.2006.08.038 PMID: 17184840
6.  Recchia FM, Busbee BG, Pearlman RB, Carvalho-Recchia CA, Ho AC. Changing trends in the microbiologic aspects of postcataract endophthalmitis. Arch Ophthalmol. 2005; 123: 341–346. doi: 10.1001/archopht.123.3.341 PMID: 15767476
7.  Wu PC, Li M, Chang SJ, Teng MC, Yow SG, Shin SJ, et al. Risk of endophthalmitis after cataract surgery using different protocols for povidone-iodine preoperative disinfection. J Ocul Pharmacol Ther. 2006; 22: 54–61. doi: 10.1089/jop.2006.22.54 PMID: 16503776
8. Dave VP, Pathengay A, Schwartz SG, Flynn HW Jr. Endophthalmitis following pars plana vitrectomy: a literature review of incidence, causative organisms, and treatment outcomes. Clin Ophthalmol. 2014; 8: 2183–2188. doi: 10.2147/OPTH.S72939 PMID: 25382968

9. Holland EJ, McDonald MB, Parekh JG, Sheppard JD. Antibiotic resistance in acute postoperative endophthalmitis. Ophthalmology. 2014; 121(11 Suppl): S1–S9. doi: 10.1016/j.ophtha.2014.06.049 PMID: 25283879

10. Grzybowski A, Kuklo P, Pieczynski J, Beiko G. A review of preoperative manoeuvres for prophylaxis of endophthalmitis in intraocular surgery: topical application of antibiotics, disinfectants, or both? Current Opinion in Ophthalmology. 2016; 27(1): 9–23. doi: 10.1097/ICO.0000000000000216 PMID: 26569521

11. Gordon-Bennett P, Karas A, Flanagan D, Stephenson C, Hingorani M. A survey of measures used for the prevention of postoperative endophthalmitis after cataract surgery in the United Kingdom. Eye. 2008; 22: 620–627. doi: 10.1038/sj.eye.6702675 PMID: 17173008

12. Vazirani J, Basu S. Role of topical, subconjunctival, intracameral, and irrigative antibiotics in cataract surgery. Curr Opin Ophthalmol. 2013; 24: 60–65. doi: 10.1097/ICO.0b013e32835a93be PMID: 23080014

13. Endophthalmitis Study Group, European Society of Cataract & Refractive Surgeons. Prophylaxis of postoperative endophthalmitis following cataract surgery: results of the ESCRS multicenter study and identification of risk factors. J Cataract Refract Surg. 2007; 33: 978–988. doi: 10.1016/j.jcrs.2007.02.032 PMID: 17531690

14. Kessel L, Flesner P, Andresen J, Erngaard D, Tendal B, Hjortdal J. Antibiotic prevention of postcataract endophthalmitis: a systematic review and meta-analysis. Acta Ophthalmol. 2015; 93: 303–317. doi: 10.1111/aos.12684 PMID: 25779209

15. Rush SW, Vu D, Rush RB. The safety and efficacy of routine administration of intracameral vancomycin during cataract surgery. J Ophthalmol. 2015; Article ID: 813697. doi: 10.1155/2015/813697 PMID: 26617996

16. Anijeet DR, Palimar P, Peckar CO. Intracameral vancomycin following cataract surgery: an eleven-year study, Clin Ophthalmol. 2010; 4: 321–326. PMID: 20463800

17. Shorstein NH, Winthrop KL, Herrinton LJ. Decreased postoperative endophthalmitis rate after institution of intracameral antibiotics in a Northern California eye department. J Cataract Refract Surg. 2013; 39: 8–14. doi: 10.1016/j.jcrs.2012.07.031 PMID: 23036356

18. Haripriya A, Chang DF, Nambur S, Smita A, Ravindran RD. Efficacy of intracameral moxifloxacin endophthalmitis prophylaxis at Aravind Eye Hospital. Ophthalmol. 2016; 123: 302–308. doi: 10.1016/j.ophtha.2015.09.037 PMID: 26522705

19. Matsuura K, Miyoshi T, Suto C, Akura J, Inoue Y. Efficacy and safety of prophylactic intracameral moxifloxacin injection in Japan. J Cataract Refract Surg. 2013; 39: 1702–1706. doi: 10.1016/j.jcrs.2013.05.036 PMID: 24054967

20. Friling E, Lundström M, Stenevi U, Montan P. Six-year incidence of endophthalmitis after cataract surgery: Swedish national study. J Cataract Refract Surg. 2013; 39: 15–21. doi: 10.1016/j.jcrs.2012.10.037 PMID: 23245359

21. Galvis V, Tello A, Sánchez MA, Camacho PA. Cohort study of intracameral moxifloxacin in postoperative endophthalmitis prophylaxis. Ophthalmol Eye Dis. 2014; 6: 1–4. doi: 10.4137/OED.S13102 PMID: 24526838

22. Hartling L, Milne A, Hamm MP, Vandermeer B, Ansari M, Tsertsivadze A, et al. Testing the Newcastle Ottawa scale showed low reliability between individual reviewers. J Clin Epidemiol. 2013; 66: 982–993. doi: 10.1016/j.jclinepi.2013.03.003 PMID: 23683848

23. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions Version 5.1.0 (updated March 2011), The Cochrane Collaboration 2011. Available: http://www.cochrane-handbook.org/.

24. Jabbarvand M, Hashemian H, Khodaparast M, Jouhari M, Tabatabaei A, Rezaei S. Endophthalmitis occurring after cataract surgery: outcomes of more than 480 000 cataract surgeries, epidemiologic features, and risk factors. Ophthalmology. 2016; 123: 295–301. doi: 10.1016/j.jcrs.2015.08.023 PMID: 26704822

25. Ta CN, Chan I, Dhatt HS, Paterno J, Fisher E, Singh K, et al. Prospective comparison of topical moxifloxacin in eliminating conjunctival bacterial flora following a one-day or one-hour application. J Ocul Pharmacol Ther. 2008; 24: 427–431. doi: 10.1089/jop.2008.0018 PMID: 18665815

26. Moss JM, Nguyen D, Liu YI, Singh K, Montague A, Egbert PR et al. Comparison of one-day versus one-hour application of topical gatifloxacin in eliminating conjunctival bacterial flora. Ophthalmol. 2008; 115: 2013–2016. doi: 10.1016/j.ophtha.2008.06.024 PMID: 18708260
27. Yu-Wai-Man P, Morgan SJ, Hildreth AJ, Steel DH, Allen D. Efficacy of intracameral and subconjunctival cefuroxime in preventing endophthalmitis after cataract surgery. J Cataract Refract Surg. 2008; 34: 447–451. doi: 10.1016/j.jcrs.2007.10.041 PMID: 18299070

28. Tan CSH, Wong HK, Yang FP. Epidemiology of postoperative endophthalmitis in an Asian population: 11-year incidence and effect of intracameral antibiotic agents. J Cataract Refract Surg. 2012; 38: 425–430. doi: 10.1016/j.jcrs.2011.09.040 PMID: 22245169

29. Asencio MA, Huertas M, Carranza R, Tenias JM, Celis J, Gonzalez-del Valle F. Impact of changes in antibiotic prophylaxis on postoperative endophthalmitis in a Spanish hospital. Ophthal Epidemio. 2014; 21: 45–50. doi: 10.3109/09286586.2013.867511 PMID: 24467562

30. Coskun M, Altintas AG, Anayol MA, Raza S, Celikbilek N, Simsek S. Evaluation of efficacy of topical povidone-iodine and different types of fluoroquinolones in the sterilization of bacterial flora on the conjunctiva. J Ocul Pharmacol Ther. 2011; 27: 589–592. doi: 10.1089/jop.2010.0192 PMID: 21834670

31. Halachmi-Eyal O, Lang Y, Keness Y, Miron D. Preoperative topical moxifloxacin 0.5% and povidone-iodine 5.0% versus povidone-iodine 5.0% alone to reduce bacterial colonization in the conjunctival sac. J Cataract Refract Surg. 2009; 35: 2109–2114. doi: 10.1016/j.jcrs.2009.06.038 PMID: 19969216

32. Miño de Kaspar H, Kreutzer TC, Aguierre-Romo I, Ta CN, Dudichum M, et al. A prospective randomized study to determine the efficacy of preoperative topical levofloxacin in reducing conjunctival bacterial flora. Am J Ophthalmol. 2008; 145: 136–142. doi: 10.1016/j.ajo.2007.08.031 PMID: 17996212

33. Li B, Miño de Kaspar H, Hartloglou C, Kook D, Kampik A, Sheng M et al. Comparison of 1-day versus 1-hour application of topical neomycin/polymyxin-B before cataract surgery. J Cataract Refract Surg. 2015; 41: 724–731. doi: 10.1016/j.jcrs.2014.06.042 PMID: 25840297

34. Inoue Y, Usui M, Ohashi Y, Shiota H, Yamazaki T. Preoperative disinfection of the conjunctival sac with antibiotics and iodine compounds: a prospective randomized multicenter study. Jpn J Ophthalmol. 2008; 52: 151–161. doi: 10.1007/s10384-008-0517-y PMID: 18661264

35. He L, Ta CN, Hu N, Sinnar S, Miño de Kaspar H. Prospective randomized comparison of 1-day and 3-day application of topical 0.5% moxifloxacin in eliminating preoperative conjunctival bacteria. J Ocul Pharmacol Ther. 2009; 25: 373–378. doi: 10.1089/jop.2008.0102 PMID: 19492956

36. Ta CN, Egbert PR, Singh K, Shriver EM, Blumenkranz MS, Miño De Kaspar H. Prospective randomized comparison of 3-day versus 1-hour preoperative ofloxacin prophylaxis for cataract surgery. Ophthalmol. 2002; 109: 2036–2040. doi: 10.1016/S0161-6420(02)01236-8

37. Ta CN, Sinnar S, He L, Myung D, Miño De Kaspar H. Prospective randomized comparison of 1-day versus 3-day application of topical levofloxacin in eliminating conjunctival flora. Eur J Ophthalmol. 2007; 17: 689–695. PMID: 17932841

38. Rudnisky CJ, Wan D, Weis E. Antibiotic choice for the prophylaxis of post-cataract extraction endophthalmitis. Ophthalmology. 2014; 121(4):835–41. doi: 10.1016/j.ophtha.2013.08.046 PMID: 24326107

39. Cao H, Zhang L, Li L, Lo S. Risk factors for acute endophthalmitis following cataract surgery: a systematic review and meta-analysis. PLoS One. 2013; 8: e71731. doi: 10.1371/journal.pone.0071731 PMID: 23990980

40. Moshirfar M, Feiz V, Vitale AT, Wegelin JA, Basavanthappa S, Wolsey DH. Endophthalmitis after uncomplicated cataract surgery with the use of fourth-generation fluoroquinolones: a retrospective observational case series Ophthalmol. 2007; 114: 686–691. doi: 10.1016/j.ophtha.2006.08.038 PMID: 17184840

41. Bucci FA, Amico LM, Evans RE. Antimicrobial efficacy of prophylactic gatifloxacin 0.3% and moxifloxacin 0.5% in patients undergoing phacoemulsification surgery. Eye Contact Lens. 2008; 34: 39–42. doi: 10.1097/ICL.0b013e3180d459d1 PMID: 18190882