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· Meta-Analysis ·

Incidence of endophthalmitis after phacoemulsification cataract surgery: a Meta-analysis

Si-Lu Shi[1], Xiao-Ning Yu[1], Yi-Lei Cui[1], Si-Fan Zheng[2], Xing-Chao Shentu[1]

[1]Eye Center of the Second Affiliated Hospital of Zhejiang University, School of Medicine, Hangzhou 310009, Zhejiang Province, China
[2]GKT School of Medical Education, King's College London, London SE1 1UL, England, UK
Correspondence to: Xing-Chao Shentu. Eye Center of the Second Affiliated Hospital of Zhejiang University, School of Medicine, 88 Jiefang Road, Hangzhou 310009, Zhejiang Province, China. stxc@zju.edu.cn
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Abstract
● **AIM:** To evaluate the overall endophthalmitis incidence and the effectiveness of potential prophylaxis measures following phacoemulsification cataract surgery (PCS).
● **METHODS:** The PubMed and Web of Science databases were searched from inception to April 30th, 2021. We included studies that reported on the incidence of endophthalmitis following PCS. The quality of the included studies was critically evaluated with the Newcastle-Ottawa quality assessment scale. The random effect or the fixed-effects model was used to evaluated the pooled incidence based on the heterogeneity. The publication bias was assessed by Egger's linear regression and Begg's rank correlation tests.
● **RESULTS:** A total of 39 studies containing 5 878 114 eyes were included and critically appraised in the Meta-analysis. For overall incidence of endophthalmitis after PCS, the Meta-analysis yielded a pooled estimate of 0.092% (95%CI: 0.083%-0.101%). The incidence appeared to decrease with time (before 2000: 0.097%, 95%CI: 0.060%-0.135%; 2000 to 2010: 0.089%, 95%CI: 0.076%-0.101%; after 2010: 0.063%, 95%CI: 0.050%-0.077%). Compared with typical povidone-iodine solution (0.178%, 95%CI: 0.071%-0.285%) and antibiotics subconjunctival injections (0.047%, 95%CI: 0.001%-0.095%), the use of intracameral antibiotics significantly reduced the incidence of endophthalmitis after PCS (0.045%, 95%CI: 0.034%-0.055%, RR: 7.942, 95%CI: 4.510-13.985).
● **CONCLUSION:** Due to the advancement of phacoemulsification technology and the widespread use of intracameral antibiotics, the incidence of endophthalmitis following PCS shows a decreasing trend over time. The use of intracameral antibiotics administration will significantly reduce the risk of endophthalmitis.
● **KEYWORDS:** endophthalmitis; phacoemulsification cataract surgery; intracameral antibiotics; antibiotics subconjunctival injections; typical povidone-iodine solution; Meta-analysis
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INTRODUCTION
Cataract surgery is one of the most commonly performed intraocular operation across the world. Over the past few decades, phacoemulsification has gradually replaced extracapsular extraction as the main cataract surgery techniques[1]. Compared with other cataract surgery techniques, phacoemulsification is generally considered a safe procedure with fewer complications and rapid visual rehabilitation[2]. However, surgical complications do still occur.

Among all the phacoemulsification complications, postoperative endophthalmitis continues to be the most serious one, and can usually lead to devastating effects on visual outcomes, even eye enucleation[3]. It is acutely caused by microorganisms introduced to the interior of the eye during or after the surgery. The infection's rate severity of spread depends on the pathogenic microorganisms' load and virulence[4]. A variety of risk factors were reported to have an impact on endophthalmitis after phacoemulsification cataract surgery (PCS), including the insertion method and material of intraocular lens[5], preoperative conjunctival sac disinfection[6], use of intracameral antibiotics[7], incision location[8], and patient age[9]. Although the reported incidence of infectious endophthalmitis after PCS is relatively low, between 0.013% to 0.7%[9-10], the increasing number of phacoemulsification procedures across the world and severe outcomes poses a serious public health issue.

To date, several Meta-analyses have been conducted to summarize clinical risk factors of endophthalmitis or evaluate the effectiveness of intracameral antibiotics for prophylaxis against endophthalmitis following cataract surgery[8,11-13]. However, no prior literature has distinguished data for PCS, which is becoming the most mainstream cataract procedure. The overall incidence of endophthalmitis and potential prophylaxis measures should be evaluated to provide guidelines for further clinical work and strengthen the evidence base for establishing international guidelines. We, therefore, conducted this Meta-analysis on the current relevant studies to determine a more accurate incidence of endophthalmitis and establish more informed conclusions about this infrequent but devastating complication after PCS.

Method This Meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement standards[14].

Search Strategy Two independent reviewers (Shi SL and Yu XN) conducted a systematic literature search on PubMed and Web of Science databases for eligible articles published up to April 30th 2021. The literature search strategy included: “cataract surgery” or “phacoemulsification” and “endophthalmitis”. A manual search of potentially eligible studies was also conducted in the reference lists within both original and relevant review articles.

Eligibility Criteria Studies that met the following inclusion criteria were included in the present systematic review and Meta-analysis: 1) prospective or retrospective studies evaluating the incidence of endophthalmitis after cataract surgery; 2) phacoemulsification technique was used for the removal of cataracts.

Studies were excluded if 1) could not provide sufficient data on the primary outcomes for analysis; 2) were not published in English; 3) were reviews, experimental studies, case series, editorials, letters to the editor, duplicate studies, or conference abstracts; 4) sample size is less than 1000. As the rate of post-phacoemulsification endophthalmitis is estimated to be less than 0.1% (or 1 in 1000 participants). Therefore, any study with less than 1000 eyes may artificially overestimate the incidence.

Data Extraction and Quality Assessment Two independent reviewers (Shi SL and Yu XN) identified the following relevant data from each included study: first author’s name, publication year, study period, sample size, characteristics of participants (age, % females), endophthalmitis incidence, and other related information. For studies including overlapping data, only the most recent or the most informative set was included. Any discrepancies were resolved by mutual discussion. The quality of the included studies was evaluated using the Newcastle-Ottawa quality assessment scale (NOS). A study with a score of ≥5 was defined as a high-quality study in this Meta-analysis[15].

Data Synthesis and Analysis Meta-analysis was conducted for each outcome reported in more than two studies. Heterogeneity among included studies was evaluated by Cochran’s Q statistic and I^2 index score. Values of I^2> 50% or P>0.1 was considered as high heterogeneity. When heterogeneity was high, random effects (DerSimonian and Laird method) were used as the analysis model, otherwise, the fixed-effects model (inverse variance method) was used[16-17]. The pooled incidence of post-phacoemulsification endophthalmitis was measured, and the outcome was reported with a 95% confidence interval (CI). Subgroup estimates by the use of intracameral antibiotics, antibiotics subconjunctival injections, and typical povidone-iodine solution, as well as the data collection period, were also conducted. We also compared the post-phacoemulsification endophthalmitis incidence between the intracameral antibiotics group and the non-intracameral antibiotics group with relative risk (RR) values. A sensitivity analysis was performed to assess the robustness of the main Meta-analysis results. The publication bias was assessed by Egger’s linear regression and Begg’s rank correlation tests[18-19]. All statistical analyses were conducted using Stata 12.0 software (Stata Corporation, College Station, TX, USA).

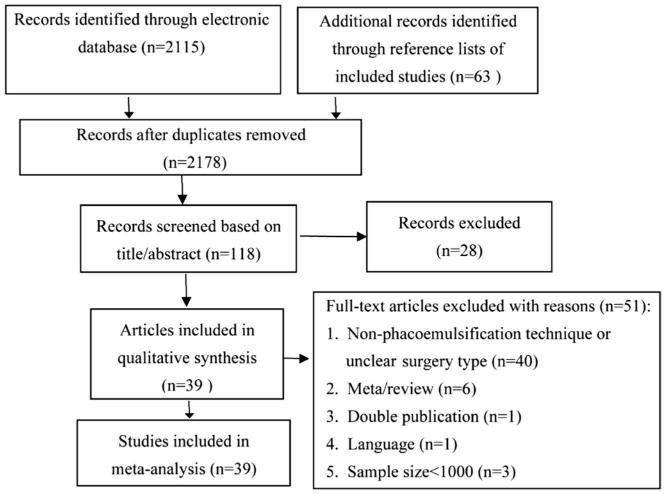

Figure 1 Preferred reporting items for systematic reviews and Meta-analysis flow diagram of the literature search process.

RESULTS

The study screening process is described in the PRISMA flow diagram in Figure 1. After the removal of duplicates, our systematic search strategy identified 2115 potentially relevant studies. After initial screening based on the title and abstract, a total of 90 studies were reviewed in full text. Of these studies, fifty-one articles were excluded for the following reasons: forty were non-phacoemulsification technique or could not provide surgery type details, six were Meta-analysis or reviews, one had a duplicated population with another study, three had a sample size of fewer than 1000 eyes, and one was published in a non-English language. A total of 39 studies were included in the final analysis (Figure 1)[4-5,7,10,13,20-54].

Table 1 Overview on the characteristics of the included studies

Study ID	Publication year	Data collection period	Country	Continent	Age (y)	Sex (% female)	NOS assessment
Montan *et al*	2002	1996.2-2000.12	Sweden	Europe	57-92	80	7
Montan *et al*	2002	1998	Sweden	Europe	Mean 69.10	66.4	7
Mayer *et al*	2003	1991.6-2001.6	UK	Europe	43-89	73	7
Colleaux *et al*	2000	1994.9-1998.1	Canada	North America	-	-	7
Nagaki *et al*	2003	1998.3-2001.3	Japan	Asia	50-96	61	7
Li *et al*	2004	1980-2000	Australia	Oceania	Include >80	58	7
Miller *et al*	2005	2000.2-2004.11	UK	Europe	50-83	-	7
Wejde *et al*	2005	1999-2001	Sweden	Europe	Include >85	66.1	7
Patwardhan *et al*	2006	1998.1-2003.12	UK	Europe	-	-	7
Romero *et al*	2006	2001.1-2004.12	Spain	Europe	53-87	57.99	7
Trinavarat *et al*	2006	2001.7-2004.12	Thailand	Asia	3-81	62.5	7
Barry *et al*	2006	2003.9-2006.1	Multiple countries	-	-	-	7
Oshika *et al*	2007	2003	Japan	Asia	-	-	7
Jensen *et al*	2008	1997.1-2007.12	USA	North America	29-91	52.5	7
Al-Mezaine *et al*	2009	1997.1-2006.12	Saudi Arabia	Asia	49-82	40	7
Garat *et al*	2009	2002.1-2007.12	Spain	Europe	-	60.4	7
Ravindran *et al*	2009	2007.1-2008.8	India	Asia	-	-	7
Ness *et al*	2011	1997.1-2008.12	Germany	Europe	53-86	37.5	7
Tan *et al*	2012	1999.6-2010.7	Singapore	Asia	Mean 72	-	7
Romero-Aroca *et al*	2012	2003.1-2009.12	Spain	Europe	53-89	58.1	8
Barreau *et al*	2012	2003.4-2008.6	France	Europe	Include >75	58.47	8
Råen *et al*	2013	2004-2011	Norway	Europe	56-94	55.5	7
Friling *et al*	2013	2005-2010	Sweden	Europe	Include >85	61.6	8
Yao *et al*	2013	2006-2011	China	Asia	2-100	55.3	7
Shorstein *et al*	2013	2007-2011	USA	North America	Median 74	-	7
Asencio *et al*	2014	2000-2008	Spain	Europe	28-92	38.4	7
Galvis *et al*	2014	2007.1-2012.12	Colombia	South America	55-79	-	7
Weston *et al*	2015	2004.4-2012.3	UK	Europe	60-89	61	7
Daien *et al*	2016	2010.2-2014.10	France	Europe	Mean 73.9	58.9	7
Haripriya *et al*	2017	2014.1-2016.5	India	Asia	-	-	7
Inoue *et al*	2018	2012.1-2013.12	Japan	Asia	Mean 73.2	58.5	8
Friling *et al*	2019	1990.2-2009.11	Sweden	Europe	-	66	7
Oh *et al*	2019	2003-2013	South Korea	Asia	39-78	59	7
Wai *et al*	2018	2008.6-2014.12	Malaysia	Asia	Median 64	34.35	7
Tuñí-Picado *et al*	2018	2010.1-2014.12	Spain	Europe	Mean 43	58.5	7
Moser *et al*	2019	2002.1-2017.12	Spain	Europe	-	-	7
Chen *et al*	2019	2012.10-2017.6	China	Asia	Mean 72	64	8
Li *et al*	2019	2012.3-2017.4	USA	North America	-	-	7
Kim *et al*	2019	2014.7-2017.6	Korea	Asia	Mean 69.1	57.43	7

Description of Search Results Characteristics of all the included studies are summarized in Table 1. The total sample size for these studies was 5 878 114, ranging from 2674 to 2 424 038. These studies were conducted in 4 continents, with 19 in Europe, 13 in Asia, 5 in America, and 1 in Oceania. The research period ranged from 1980 to 2017, and the follow-up period ranged from 0.5 to 6mo. All included studies were considered to be high quality with the NOS score ≥5.

Overall Incidence of Endophthalmitis After Phacoemulsification Cataract Surgery A total of 39 studies were included in the analysis of overall incidence of endophthalmitis after PCS. Of the 5 878 114 included eyes, 4061 had endophthalmitis after PCS, the pooled estimated incidence was 0.107% (95%CI: 0.097%-0.116%, Pheterogeneity<0.001; Begg's P=0.60, Egger's P=0.67). The results of sensitivity analysis by sequentially omitting individual

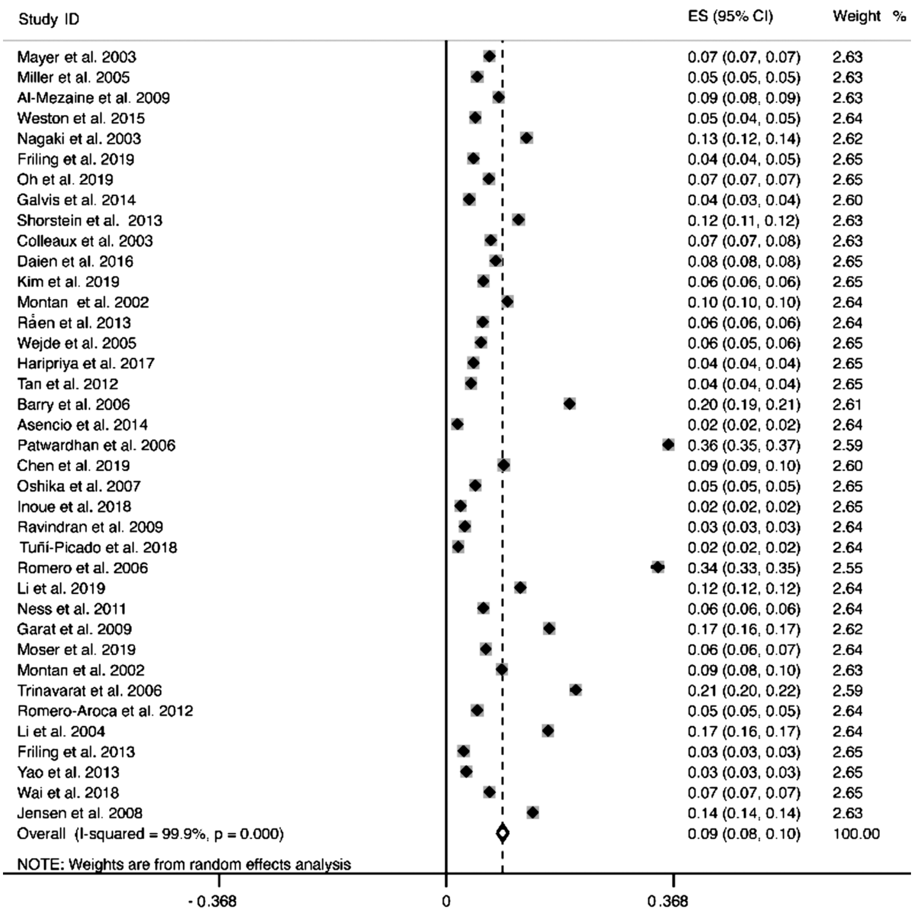

Figure 2 Forest plot and the overall estimates of the incidence of endophthalmitis after phacoemulsification cataract surgery.

study identified one study that altered the significance of the pooled values[54], which provided an especially high incidence. After removing this study, the pooled estimated incidence was 0.092% (95%CI: 0.083%-0.101%, Pheterogeneity<0.001; Begg's P=0.561, Egger's P=0.832; Figure 2).

Incidence of Endophthalmitis Grouped by Data Collection Period We also analyzed the influence of the study period on endophthalmitis incidence. In total, 7 were conducted before 2000, 19 from 2000-2010, and 8 after 2010. The results of the subgroup analysis demonstrated a decreased trend of endophthalmitis risk (before 2000: 0.097%, 95%CI: 0.060%-0.135%, Pheterogeneity<0.001, Begg's P=0.548, Egger's P=0.487; 2000 to 2010: 0.089%, 95%CI: 0.076%-0.101%, Pheterogeneity<0.001, Begg's P=0.880, Egger's P=0.435; after 2010: 0.063%, 95%CI: 0.050%-0.077%, Pheterogeneity<0.001, Begg's P=1.000, Egger's P=0.354; Figure 3).

Incidence of Endophthalmitis with Typical Povidone-iodine Solution Figure 4 summarizes the four studies including 37 431 patients that evaluated the incidence of endophthalmitis after PCS with topical povidone-iodine solution disinfecting the ocular surface. The pooled incidence was 0.178% (95%CI: 0.071%-0.285%, Pheterogeneity<0.001, Begg's P=0.308, Egger's P=0.34).

Incidence of Endophthalmitis with Antibiotics Subconjunctival Injections Three studies including 29 185 patients evaluated the incidence of endophthalmitis after PCS with antibiotics subconjunctival injections. The pooled incidence was 0.047% (95%CI: 0.001%-0.095%, Pheterogeneity<0.001, Begg's P=0.296, Egger's P=0.150; Figure 4).

Incidence of Endophthalmitis with Intracameral Antibiotics Sixteen studies including 391 359 eyes reported endophthalmitis data after PCS with intracameral antibiotics. One study reporting the rate of 0 was excluded[27]. The overall pooled estimated incidence was 0.045% (95%CI: 0.034%-0.055%, Pheterogeneity<0.001, Begg's P=0.553, Egger's P=0.553; Figure 4). Nine studies were involved in providing the results of a Meta-analysis for comparing the rate of endophthalmitis after PCS with intracameral antibiotics versus the rate without intracameral antibiotics. There were 150 227 and 189 855 eyes in the intracameral antibiotics group and non-intracameral antibiotics group, respectively. The overall RR was 7.942% (95%CI: 4.510%-13.985%, Pheterogeneity=0.01, Begg's P=0.348, Egger's P=0.376; Figure 5). The sensitivity analysis did not alter the significance of pooled estimates of these two analyses.

In studies included in this Meta-analysis, three antibiotics were used in endophthalmitis prophylaxis after PCS alone.

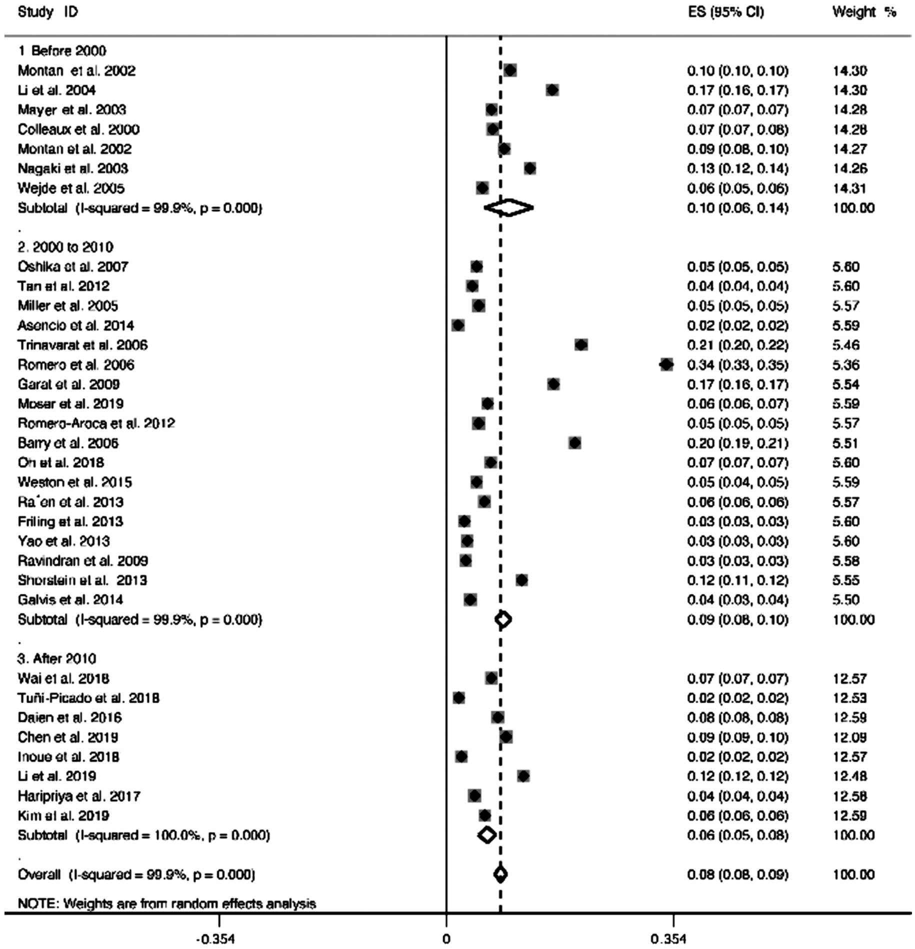

Figure 3 Subgroup analysis of incidence of endophthalmitis grouped by data collection period.

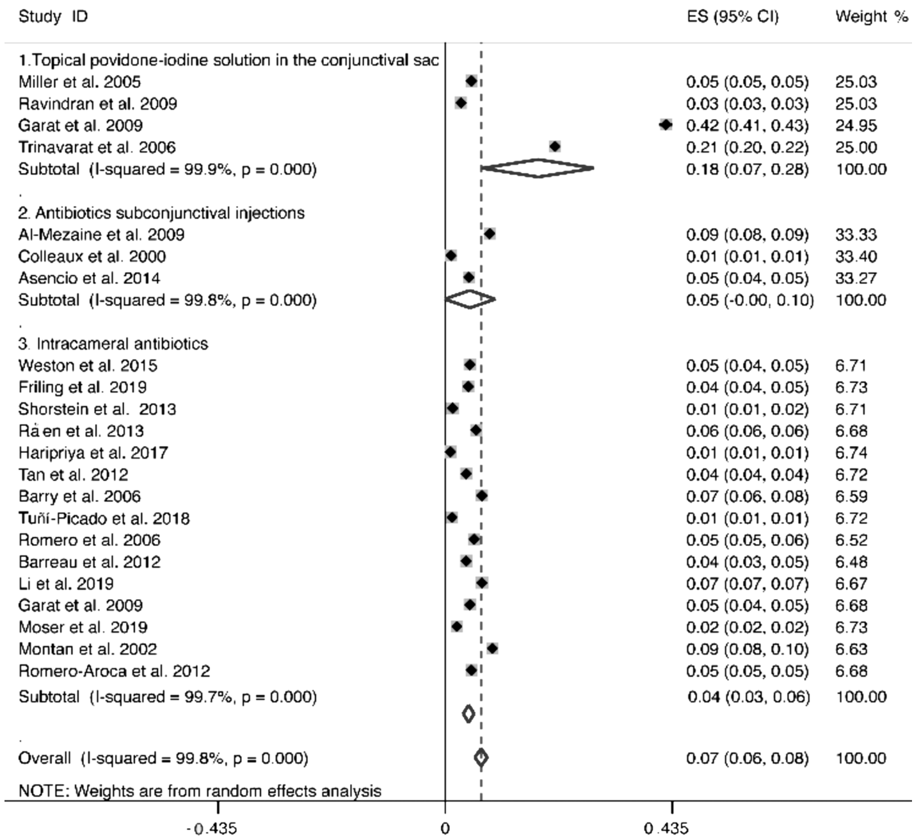

Figure 4 Incidence of endophthalmitis with typical povidone-iodine solution disinfection, antibiotics subconjunctival injections or intracameral antibiotics injections.

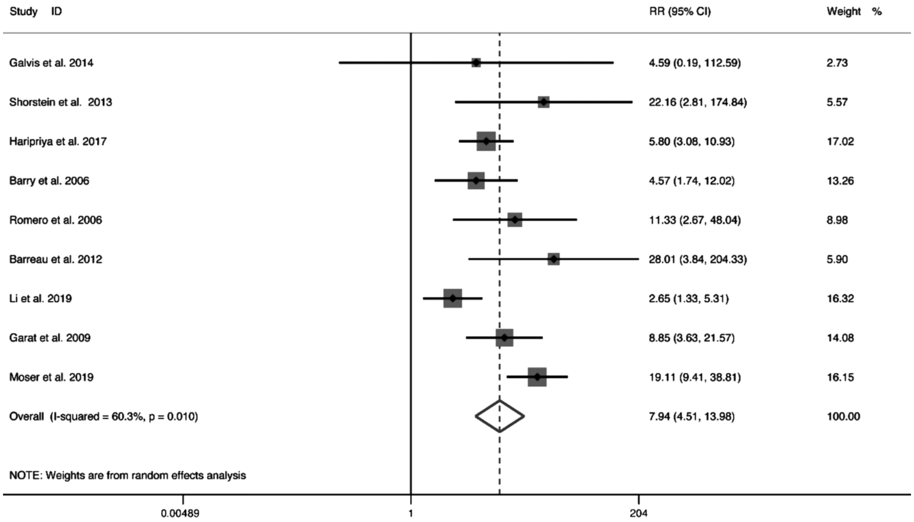

Figure 5 Risk ratio estimates of intracameral antibiotics treatment for incidence of endophthalmitis.

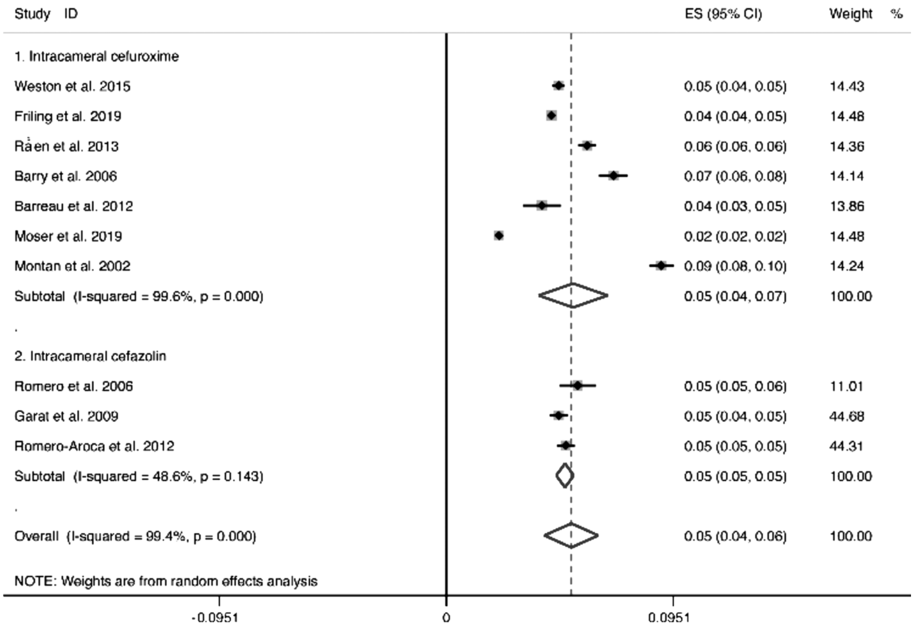

Figure 6 Incidence of endophthalmitis with intracameral cefuroxime or cefazolin.

In total, 7 studies involving 187 232 patients reported endophthalmitis incidence with intracameral cefuroxime, and the pooled incidence was 0.053% (95%CI: 0.039%-0.068%, $P_{heterogeneity}<0.001$, Begg's $P=0.764$, Egger's $P=0.782$; Figure 6); 3 studies involving 29 572 patients reported endophthalmitis incidence with intracameral cefazolin, and the pooled incidence was 0.049% (95%CI: 0.047%-0.052%, $P_{heterogeneity}=0.143$, Begg's $P=1.000$, Egger's $P=0.441$; Figure 6). Two studies reported endophthalmitis incidence with intracameral moxifloxacin, with one study with 1618 patients reported 0 cases of endophthalmitis[27], and the other study reporting an incidence of 0.01%[7].

DISCUSSION

With 39 studies included, the present Meta-analysis provides the most comprehensive profile for the endophthalmitis incidence after PCS at the global level. The overall data-driven estimate of endophthalmitis incidence was 0.092%. Based on the data collection timeframe, between 1990 to 1999, 2000 to 2009, and 2010 to present, the pooled incidence was 0.097%, 0.089% and 0.063%, respectively, showing a decreasing trend. This was mainly due to the improvement of the operative techniques, the advances in the intraocular lens, and the adoption of pre- and post-operative prophylaxis strategies.

As the number of PCS performed worldwide continues to increase, prophylaxis strategies have become a serious public health issue. Several measures have been suggested to decrease the risk of endophthalmitis after PCS, such as pre- and post-operative topical antibiotics, preoperative typical povidone-iodine, intracameral and subconjunctival antibiotic injection, and antibiotic-containing irrigation fluid[7]. In this study, we evaluated the effectiveness of three prophylactic measures, including topical povidone-iodine solution disinfecting the ocular surface, antibiotics subconjunctival injections, and intracameral antibiotics. The pooled incidence indicated that intracameral antibiotics were the most effective with the endophthalmitis incidence significantly declining to 0.045%, a reduction of 6.9 times compared to PCS when intracameral antibiotics were not used.

From this study, evidence was clear that intracameral antibiotics could significantly help reduce the endophthalmitis risk after PCS. Intracameral antibiotics are now widely accepted and used during cataract surgery globally. According to results from 2021 American Society of Cataract and Refractive Surgery, intracameral antibiotics is suggested as an efficacious method of endophthalmitis prophylaxis[55]. Although the use of intracameral antibiotics has been recognized in the Preferred Practice Pattern guidelines from the American Academy of Ophthalmology, it is notable that no international ophthalmological society has advocated strongly for the use of a certain type of antibiotic. In this meta-analysis, two antibiotics (cefazolin and cefuroxime) were evaluated. Of the two, cefuroxime was the most commonly used antibiotics, though frequency of use and choice of antibiotic vary considerably throughout the world[56]. Cefuroxime was also reported to be the most effective antibiotic in perioperative prophylaxis for endophthalmitis following all types of cataract surgery with a pooled incidence of 0.09% in a Meta-analysis[13]. However, according to our results, cefazolin is more effective than cefuroxime with a pooled incidence of 0.049%, compared to cefuroxime's pooled incidence of 0.053%. It is reasonable considering that, cefazolin is more sensitive for gram-negative bacteria, which is the most common ocular bacterial flora in human conjunctival sac[57].

There is also no established standard for injection volumes and concentrations of intracameral antibiotics. In the studies included in this Meta-analysis, the reported moxifloxacin concentration was 0.05 to 0.5 mg per 0.1 mL, cefuroxime concentration was 1 mg per 0.1 mL, and cefazolin concentration was from 1 to 2.5 mg per 0.1 mL, with an injection volume ranging from 0.03 mL to 0.1 mL. An *in vitro* study incubating bacteria isolated from endophthalmitis cases and the healthy conjunctival sac confirmed that bactericidal activity of intracameral antibiotics was concentration-dependent[58]. It is worth noticing that besides the administration dosage, anterior chamber volume is another important factor that determines the final drug concentrations. Cataract patients with larger anterior segments result in relatively lower drug concentrations with a given dose[59]. Intraocular toxicity of intracameral antibiotics should also be taken into consideration. Studies have reported that excessive use of high amounts of intracameral cefuroxime may cause macular edema, anterior and posterior segment inflammation, retinal vascular leakage and/or infarction, uveitis, and a decrease in long-term retinal function[60].

Our Meta-analysis may have some limitations. The assessment of endophthalmitis, varied among the studies, contributes to increased heterogeneity. Studies that only reported endophthalmitis diagnosed based on the culture result of pathogenic microorganism tended to underestimate the incidence. The fairly low incidence of endophthalmitis after PCS also requires the analysis of a very large sample size for an accurate estimate. Finally, the limited sample size in subgroup analysis was too few to improve the accuracy of results.

In conclusion, we assessed the incidence of endophthalmitis after PCS in this Meta-analysis. The incidence shows a decreasing trend over the past 30y, resulting in a total 1/3 reduction. We also found strong and consistent evidence that intracameral antibiotics administration during PCS would significantly reduce the risk of endophthalmitis. This study provided an informative data source for evidence-based public health interventions.

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