Evidence Brief: Intracameral Moxifloxacin for Prevention of Endophthalmitis After Cataract Surgery

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AUTHORS

Author roles, affiliations, and contributions to the present report (using the CRediT taxonomy) are summarized in the table below.

Author	Role and Affiliation	Report Contribution
Johanna Anderson, MPH	Senior Research Associate, Evidence Synthesis Program (ESP) Coordinating Center, Portland VA Health Care System Portland, OR	Investigation, Methodology, Supervision, Project administration, Data curation, Writing – original draft, Writing – review & editing
Sarah Young, MPH	Research Associate, ESP Coordinating Center, Portland VA Health Care System Portland, OR	Investigation, Data curation, Writing – review & editing
Glen Cockerham, MD	National Director, VHA Ophthalmology Program Office, VA Palo Alto Health Care System Palo Alto, CA	Conceptualization, Investigation, Writing – review & editing
Amy Chomsky, MD	Chief of Ophthalmology, VA Tennessee Valley Healthcare System Nashville, TN	Conceptualization, Investigation, Writing – review & editing
Nicholas J. Parr, PhD, MPH	Associate Director, ESP Coordinating Center, Portland VA Health Care System Portland, OR	Conceptualization, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing

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The findings and conclusions in this document are those of the author(s) who are responsible for its contents and do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted health care topics of importance to clinicians, managers, and policymakers as they work to improve the health and health care of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program comprises four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, interface with stakeholders, and address urgent evidence needs. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

The present report was developed in response to a request from VHA Ophthalmology Program Office. The scope was further developed with input from Operational Partners (below) and the ESP Coordinating Center review team.

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Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

Amy Chomsky, MD
Chief of Ophthalmology
VA Tennessee Valley Healthcare System

Glenn Cockerham, MD
National Director
VHA Ophthalmology Program Office

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EXECUTIVE SUMMARY

Key Findings

- Intracameral moxifloxacin use is associated with a 73% reduction in odds of endophthalmitis compared to standard care (OR = 0.27, 95% CI [0.19, 0.40], $p < .0001$), based on a meta-analysis of 14 comparative studies of 3,566,022 eyes.
- Intracameral moxifloxacin appears to be safe at the dosages and preparations reported, with no studies reporting adverse events directly related to moxifloxacin use.
- Odds of endophthalmitis after cataract surgery did not significantly differ with use of intracameral moxifloxacin compared to intracameral cefuroxime (OR = 1.34, 95 CI [0.73, 2.45], $p = 0.25$), based on a meta-analysis of 5 comparative studies of 847,070 eyes.
- Rigorous studies conducted in US settings may increase support for broadening use of intracameral moxifloxacin in place of or alongside topical antibiotics.
- Consistent policies, procedures, and access to standardized preparations of moxifloxacin for intracameral use are important for expanding use of intracameral moxifloxacin within the VHA.

Background

The Evidence Synthesis Program Coordinating Center is responding to a request from the VHA Ophthalmology Program Office for an Evidence Brief on intracameral moxifloxacin for preventing endophthalmitis after cataract surgery. Findings from this Evidence Brief will be used to inform VA clinical practice and related policy on intracameral moxifloxacin use for preventing endophthalmitis after cataract surgery.

Methods

To identify studies, we searched MEDLINE®, Cochrane Database of Systematic Reviews, CINAHL, and other sources up to January 2022. We used prespecified criteria for study selection, data abstraction, and rating internal validity and strength of the evidence. See the Methods section and our PROSPERO protocol for full details of our methodology.

Endophthalmitis is a rare, serious infection of the eye that can lead to permanent loss of vision. Topical antibiotic eyedrops are often prescribed to prevent endophthalmitis after cataract surgery. However, efficacy of topical drops is unclear, and there are also concerns about patient adherence to regular use of drops in the postsurgical period. In contrast to topical drops, intracameral antibiotics are administered only once (at the end of the surgical procedure after intraocular lens insertion). Prior studies have found that several antibiotics available for intracameral delivery, including cefuroxime, vancomycin, and moxifloxacin, may be beneficial for preventing endophthalmitis when delivered intracamerally. Due to concerns around antibiotic resistance and potential adverse events from use of cefuroxime and vancomycin, moxifloxacin has more recently been investigated.

Outside of the United States, moxifloxacin and other antibiotics are commercially available and commonly used in intracameral applications. Although US surgeons also routinely administer intracameral antibiotics, there are currently no antibiotics that are approved by the US Food and Drug Administration for intraocular use, and US surgeons must use repackaged and diluted topical or injectable solutions off-label. Increased risk, liability, and logistical challenges of using antibiotics off-label has led to less intracameral antibiotic use in the US compared to other countries where commercial intracameral formulations are available. Within the VHA, limited access to intracameral antibiotics has led to irregular and inconsistent usage across VHA facilities. Although several meta-analyses have reported prophylactic benefit of intracameral moxifloxacin, new evidence has emerged since the

publication of these reviews. This report synthesizes the available evidence on benefits and harms of intracameral moxifloxacin for preventing endophthalmitis after cataract surgery, with the aim of informing VHA clinical practice.

Among 21 included studies, 14 examined intracameral moxifloxacin for preventing endophthalmitis and reported occurrence of endophthalmitis after surgery (total eyes = 3,566,022). A meta-analysis of study results found that intracameral moxifloxacin use is associated with a 73% reduction in odds of endophthalmitis compared to standard care (OR = 0.27, 95% CI [0.19, 0.40], $p < .0001$). Standard care commonly included pre-, intra-, and/or postoperative use of povidone iodine with postoperative topical antibiotics and/or corticosteroids regularly used across intervention and comparator groups. Pooling results of 5 studies reporting comparative effectiveness of intracameral moxifloxacin versus intracameral cefuroxime (total eyes = 847,070); the odds of endophthalmitis did not significantly differ between antibiotic groups (OR = 1.34, 95 CI [0.73, 2.45], $p = 0.25$). Intracameral moxifloxacin also appears to be safe at the dosages and preparations reported in the studies, with no studies reporting adverse events directly related to moxifloxacin use.

These findings align with previous systematic reviews, even with the addition of 9 studies not included in previous reviews, suggesting that these results are relatively stable. However, the studies are limited by study design and study methodology. Only 1 randomized controlled trial (RCT) reported on endophthalmitis rates among the 21 included studies, and the observational studies often compared surgeries before and after introduction of intracameral moxifloxacin as a standard for endophthalmitis prophylaxis in their hospital or health system. Although most studies attempted to minimize differences between intervention groups by comparing surgeries done at a single center and/or by a single surgeon, patient and/or surgery characteristics were often unreported and may have differed after introduction of intracameral moxifloxacin. Lack of reporting and adjustment for potential confounders weakens our confidence in these findings.

Additionally, no studies were conducted in the VHA and only 4 studies were conducted within the US. Cataract surgery standards, procedures, and access to intracameral moxifloxacin vary among different countries and healthcare systems, and the available evidence may not be fully applicable to cataract surgery care in the US or VHA. Rigorous studies conducted in US settings may increase support for broader use of intracameral moxifloxacin in place of or alongside topical antibiotics, including by increasing the likelihood of FDA approval of intracameral moxifloxacin. Within the VHA, limited access to intracameral antibiotics has led to irregular and inconsistent usage across VHA facilities, and consistent policies, procedures, and access to standardized preparations of moxifloxacin for intracameral use are needed.

EVIDENCE BRIEF

INTRODUCTION

PURPOSE

The Evidence Synthesis Program Coordinating Center (ESP CC) is responding to a request from the Veterans Health Administration (VHA) Ophthalmology Program Office for an Evidence Brief on intracameral moxifloxacin for preventing endophthalmitis after cataract surgery. Findings from this brief will be used to inform VHA clinical practice and related policy on intracameral moxifloxacin use for preventing endophthalmitis after cataract surgery.

BACKGROUND

Endophthalmitis is a rare, serious infection of the eye causing inflammation and vision damage, and may lead to permanent vision loss.[1] Cataract surgery is one of the most common causes of endophthalmitis, as bacteria can enter the eye from the patients' eyelids, surgical instruments, and/or healthcare personnel during surgery.[2] Although the rate of endophthalmitis after cataract surgery in the US is low at around 0.08% to 0.14%,[3,4] the large number of cataract surgeries performed in the US and the poor visual prognosis for patients with endophthalmitis make it a serious concern.

Treatment of endophthalmitis involves systemic and locally injected antibiotics, and vitrectomy, a surgical removal of infected vitreous from the eye.[1,2] Although early treatment of endophthalmitis may improve visual outcomes, the prognosis of endophthalmitis remains poor.[2] Therefore, prevention of endophthalmitis after cataract surgery is essential to reduce the risk of poor visual outcomes. Prevention options include use of povidone iodine as a topical antiseptic, saline irrigation, and topical, oral, or injected antibiotics. Although povidone iodine is routinely used and widely accepted as a surgical antiseptic, risk of endophthalmitis remains and additional preventive measures are needed.[5,6] Topical antibiotic eyedrops, commonly along with topical steroid drops, are often prescribed to prevent endophthalmitis after cataract surgery.[5,6]

The efficacy of topical drops depends upon patient adherence and correct administration technique, and tracking of patient adherence and administration is difficult.[7] Barriers to proper administration and compliance with topical eye drops include age, physical disability, complex drug regimens that may require administration of more than 1 type of eye drop (*ie*, topical antibiotics and topic steroids), and inexperience using eye drops.[8,9] Topical eyedrop compliance may be a particular challenge among Veterans due to older age[10] and higher rates of comorbidity and disability compared to the general population.[11] In contrast to topical drops, intracameral antibiotics are administered only once (at the end of the surgical procedure after intraocular lens insertion).[4]

Intracameral antibiotics are widely used after cataract surgery to prevent endophthalmitis.[4] Common antibiotics for intracameral delivery include cefuroxime, moxifloxacin, and vancomycin.[12] In 2007, the European Association of Cataract and Refraction Surgeons (ESCRS) published a randomized controlled trial (RCT) showing effectiveness of intracameral injection of cefuroxime compared to topical antibiotics.[13] However, concerns around antibiotic resistance and adverse effects, including toxic anterior segment syndrome (TASS), a severe acute intraocular

inflammation, have led to reduced use of cefuroxime.[12,14] Similarly, vancomycin is used infrequently due to cases of vancomycin-associated hemorrhagic occlusive retinal vasculitis.[14-16] Moxifloxacin has more recently been explored to overcome the issues of antibiotic resistance and potential adverse effects, and studies have found that moxifloxacin may be beneficial for preventing endophthalmitis when delivered intracamerally after cataract surgery (compared to topical or no use of antibiotics).[14,16,17] Potential toxic effects of intracameral moxifloxacin, including endothelial cell damage and TASS, have been reported at higher doses (above 0.5 mg/mL),with the use of specific inactive ingredients (xanthan gum), and with the use of compounded moxifloxacin formulations.[18] However, intracameral moxifloxacin doses of up to 0.5 mg/0.1 mL without preservatives have been reported to be safe with no adverse effects.[15]

Intracameral antibiotics are commercially available outside of the US. However, although the American Academy of Ophthalmology has stated that there are multiple benefits to use of intracameral antibiotics after cataract surgery,[15] there are currently no antibiotics approved by the US Food and Drug Administration (FDA) for intracameral endophthalmitis prophylaxis. US cataract surgeons routinely administer intracameral antibiotics, but rely on the off-label use of topical antibiotics, which must be repackaged and diluted for intracameral injection.[15] Using antibiotics off-label for intracameral injection can pose increased risks due to errors in compounding and dilution of topical solutions, and potential adverse effects from inactive ingredients not intended for intracameral use. Due to the increased risk, liability, and logistical challenges of using antibiotics off-label, intracameral antibiotics are less widely used in the US compared to other countries where commercial intracameral formulations are available.[19] Within the VHA, limited access to antibiotics for intracameral use has led to irregular and inconsistent usage across VHA facilities. Cataract surgery is the most frequently performed surgery in the VHA, with nearly 70,000 cataract surgeries performed in fiscal year 2017,[20] and there is a need for consistent usage and preparation across VHA facilities and pharmacies.

Although several meta-analyses[14,16,17] have reported prophylactic benefit of intracameral moxifloxacin, new evidence has emerged since the publication of these reviews. This report synthesizes the available evidence on benefits and harms of intracameral moxifloxacin for preventing endophthalmitis after cataract surgery, with the aim of informing VHA clinical practice.

METHODS

PROTOCOL

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; registration number CRD42022308908).

KEY QUESTIONS

The following key questions (KQs) were the focus of this review:

KQ 1: What are the benefits and harms of intracameral moxifloxacin use during cataract surgery to prevent postoperative endophthalmitis?

KQ 2: How do benefits and harms of intracameral moxifloxacin use during cataract surgery vary based on administration method (*eg*, diluted vs undiluted) and use of co-interventions (*eg*, with vs without topical antibiotic eye drops)?

ELIGIBILITY CRITERIA

The ESP included studies that met the following criteria:

***P**opulation*	Adults undergoing cataract surgery
***I**ntervention*	Intracameral moxifloxacin use during cataract surgery
***C**omparator*	Care as usual (*ie*, no intracameral antibiotic use during cataract surgery)
***O**utcomes*	Incidence of postoperative endophthalmitis, harms (*eg*, corneal edema, severe inflammation, retinal toxicity/vasculitis), patient quality of life, patient use of co-interventions (*eg*, topical antibiotic eye drops)
***T**iming*	Any
***S**etting*	Any
***S**tudy Design*	Any, but we may prioritize articles using a best-evidence approach to accommodate Evidence Brief timeline

DATA SOURCES AND SEARCHES

To identify articles relevant to the key questions, a research librarian searched Ovid MEDLINE, CINAHL, Cochrane Database of Systematic Reviews, and ClinicalTrials.gov, as well as the AHRQ and HSR&D databases from 2016 through January 2022 using terms for *moxifloxacin* and *cataract surgery* (see Appendix A in Supplemental Materials for complete search strategies). We utilized several existing systematic reviews[14,16,17] to identify citations published prior to 2016. We limited the search to published and indexed articles involving human subjects available in the English language. Study selection was based on the eligibility criteria described above. Titles, abstracts, and full-text articles were reviewed by 1 investigator and checked by another. All disagreements were resolved by consensus or discussion with a third reviewer.

DATA ABSTRACTION AND ASSESSMENT

Effect information and population, intervention, and comparator characteristics were abstracted from all included studies. The internal validity (risk of bias) of each included study was rated using the Cochrane risk of bias tools.[21,22] All data abstraction and internal validity ratings were first completed by 1 reviewer and then checked by another; disagreements were resolved by consensus or discussion with a third reviewer. We graded the strength of the evidence for each outcome based on the AHRQ Methods Guide for Comparative Effectiveness Reviews.[23] This approach provides a rating of confidence in reported findings based on trial methodology (design, quality, and risk of bias), consistency (whether effects are in the same direction and have a consistent magnitude), precision, and directness (whether assessed outcomes are clinically important to patients and providers). For this review, we applied the following general algorithm: *high strength* evidence consisted of multiple, large trials with low risk of bias, consistent and precise findings, and clinically relevant outcomes; *moderate strength* evidence consisted of multiple trials with low to unclear risk of bias, consistent and precise findings, and clinically relevant outcomes; *low strength* evidence consisted of a single trial, or multiple small trials, with unclear to high risk of bias, inconsistent or imprecise findings, and/or outcomes with limited clinical relevance; and *insufficient* evidence consisted of a single trial with unclear or high risk of bias, or no available trials.

SYNTHESIS

Evidence on antibiotic-related adverse events was synthesized narratively due to inconsistency in measurement and reporting of these outcomes. For endophthalmitis rates, we quantitatively synthesized evidence using statistical methods appropriate for rare outcomes. For main and moderator analyses, we employed random-effects hypergeometric-normal models[24-26] to estimate effect sizes and their precision directly from count information. Moderator (mixed-effects) analyses examined whether overall effect estimates differed by surgery type. We carried out sensitivity analyses using a random-effects extension of the Peto method,[24] which is an approach intended for the analysis of rare events. Meta-analyses were conducted using the *metafor*[27] package for R (R Foundation for Statistical Computing, Vienna, Austria).

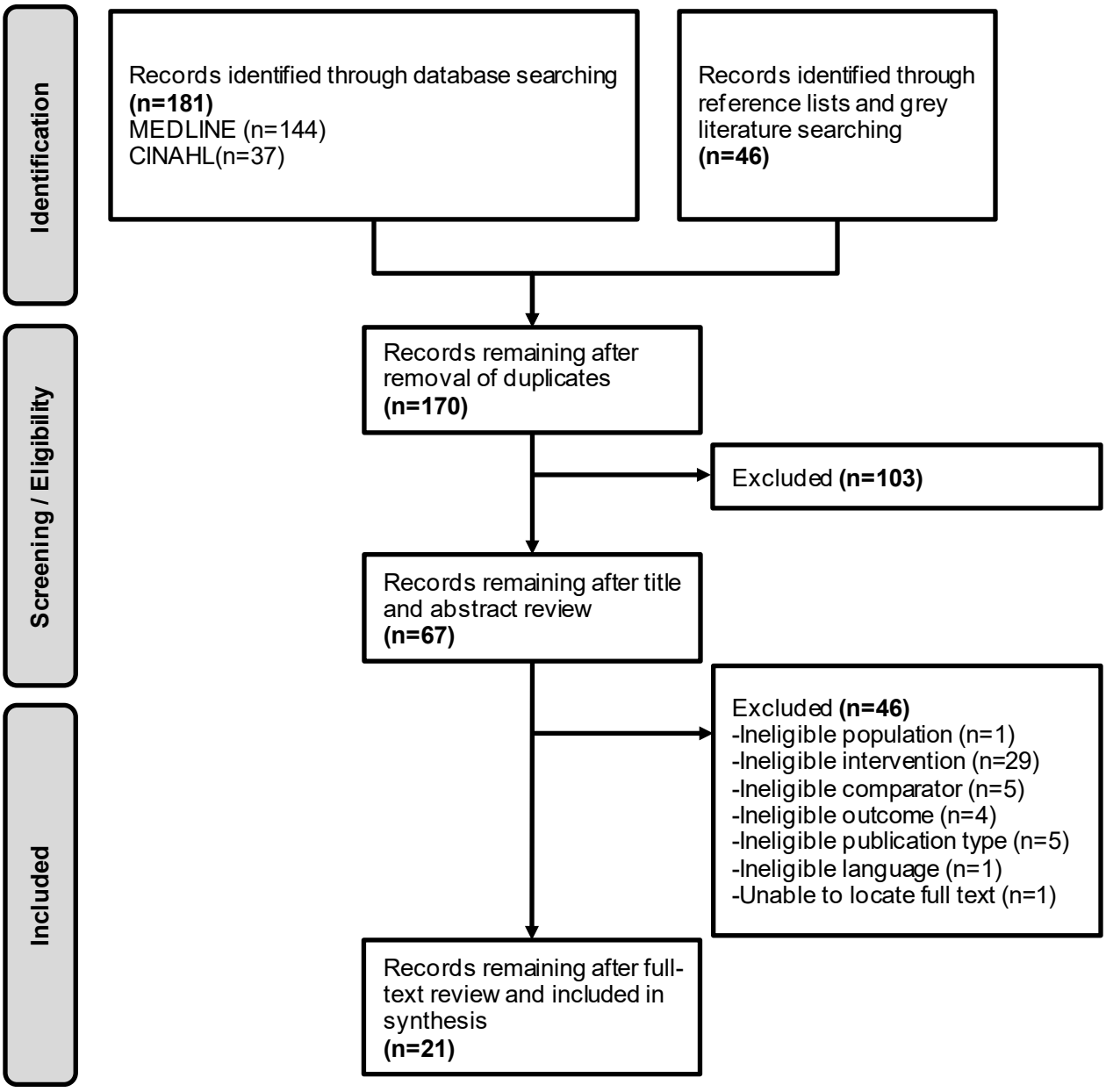
All included studies reporting endophthalmitis occurrence after intracameral moxifloxacin or standard care did so using count information, and effects are represented using odds ratios (ORs). ORs reported for sensitivity analyses were calculated using the Peto method. To increase interpretability of findings, we also estimated risk difference (RD) after intracameral moxifloxacin using a traditional random-effects model. Precision of study-level and overall estimates is reported using 95% confidence intervals (CIs), and CIs were used to evaluate statistical significance of overall estimates at a significance level of .05. For main and moderator analyses, exact CIs were calculated based on the hypergeometric-normal distribution; cluster-robust (sandwich) CIs with small-sample adjustment were employed in sensitivity analyses using the Peto method and in models estimating risk difference. Heterogeneity was estimated using maximum-likelihood estimation and is presented as 95% prediction intervals (PIs). One included study[28] reported no endophthalmitis events; to facilitate inclusion of this study in analyses, 0.5 was added to each of the study's counts. Sensitivity analyses based on the Peto method did not require this continuity correction, and we also report the main analysis with this study excluded to gauge sensitivity of our findings to the correction. No syntheses included dependent estimates (*ie*, multiple estimates from the same study in the same analysis/subgroup).

RESULTS

LITERATURE FLOW

The literature flow diagram (Figure 2) summarizes the results of the study selection process (full list of excluded studies available in Appendix B in Supplemental Materials).

Figure 1. Literature Flowchart



Abbreviations. CINAHL=Cumulative Index to Nursing and Allied Health Literature.

LITERATURE OVERVIEW

Our search identified 169 potentially relevant articles. We included 21 studies[28-48] which are summarized in Table 1 (see Appendix C in Supplemental Materials for full study details). Two studies[40,46] were RCTs, and the remaining studies were observational cohorts. Although most studies were designed to evaluate the efficacy of moxifloxacin for prevention of endophthalmitis, 5 studies[30,44-46,48] focused on the safety of moxifloxacin use. Two of these studies reported no endophthalmitis events,[45,48] while the others did not directly report endophthalmitis rates. We also identified 3 underway studies (see Appendix D in Supplemental Materials) examining intracameral moxifloxacin for endophthalmitis prophylaxis, 2 of which are RCTs.

Most studies compared intracameral moxifloxacin use to standard care without intracameral antibiotic. Standard care usually included pre-, intra-, and/or postoperative use of povidone iodine with postoperative topical antibiotics and/or corticosteroids given to all patients (intervention and comparator groups), although some studies reported varied topical antibiotic use per institution or at surgeon discretion. Several studies included comparisons to both standard care and intracameral cefuroxime,[29,31,33] while 2 studies compared intracameral moxifloxacin to intracameral cefuroxime only with no comparison to standard care.[36,42] The majority of studies were conducted outside of the US, with only 4 studies[33,42,44,46] conducted within the US. The median number of eyes examined was 40,392 (range 57 to 2,062,643). Almost all studies ($N = 19$) utilized phacoemulsification (PE) cataract surgery, with some studies also including manual small incision cataract surgery (MSCIS) or extracapsular cataract extraction (ECCE). Intracameral antibiotic dosage was commonly 0.5 mg in 0.1 mL of 0.5% moxifloxacin.

Only 2 studies were RCTs, 1 of which appeared to be well conducted,[40] while the other[46] lacked information on the randomization and allocation processes, had unclear blinding of patients, and excluded more than 15% of the initially randomized population due to loss to follow-up or adverse events unrelated to the study. Most of the observational studies examined cataract surgeries conducted within a single time period during which intracameral moxifloxacin was introduced and compared surgeries before and after the introduction of intracameral moxifloxacin. Common methodological limitations of the observational studies included lack of information on baseline patient and surgery characteristics, lack of adjustment for potential confounders, and unclear level and/or handling of missing data. Several studies had more severe methodological limitations, including comparison of data from different centers or time periods with no information or accounting for potential differences between groups, lack of adjustment for known confounders, and unclear intervention assignment (*ie*, unclear why certain patients received intracameral moxifloxacin and others did not).

Table 1. Characteristics of Included Studies

Study *Study design*	Sample Size *Follow-up*	Surgery Type	Moxifloxacin Concentration and Preparation	Comparator	Topical Antibiotic Use*	Outcomes Assessed
Arshinoff, 2011[29] *Retrospective Cohort*	N=104,914 *NR*	PE	Variable across surgical centers (0.1 to 0.5 mg MOX per 01. to 0.2 mL)	No IC antibiotic or IC cefuroxime	NR	Endophthalmitis rate
Bhatta, 2021[37]† *Retrospective Cohort*	N=11,983 *6 weeks*	PE or MSICS	0.5 mg MOX in 0.1 mL	No IC antibiotic	All patients	Endophthalmitis rate, TASS, adverse events
Cetinkaya, 2015[45] *Retrospective Cohort*	N=65 *1 year*	PE	0.1 mL of undiluted 0.5% MOX	No IC antibiotic	All patients	Corneal edema, TASS
Dave, 2022[34]† *Retrospective Cohort*	N=66,967 *6 weeks*	PE, MSICS, or ECCE	0.5 mg MOX in 0.1 mL	No IC antibiotic	All patients	Endophthalmitis rate, corneal edema, adverse events
Ekinci, 2012[30] *Retrospective Cohort*	N=60 *3 days*	PE	0.1 mL of undiluted 0.5% MOX	No IC antibiotic	All patients	Corneal edema, adverse events
Frilling, 2013[31] *Retrospective Cohort*	N=464,755 *4 weeks*	PE or "other"**	Variable across surgical centers	No IC antibiotic or IC cefuroxime	Varied	Endophthalmitis rate
Galvis, 2014[28] *Retrospective Cohort*	N=2,674 *2 weeks*	PE	0.05 mL of undiluted 0.5% MOX	No IC antibiotic	All patients	Endophthalmitis rate
Haripriya, 2016[38]† *Retrospective Cohort*	N=75,937 *6 weeks*	PE, MSICS, or ECCE	0.5 mg in 0.1 mL of 0.5% MOX	No IC antibiotic	All patients	Endophthalmitis rate, TASS, adverse events

Study ***Study design***	**Sample Size** ***Follow-up***	**Surgery Type**	**Moxifloxacin Concentration and Preparation**	**Comparator**	**Topical Antibiotic Use***	**Outcomes Assessed**
Haripriya, 2017[32] *Retrospective Cohort*	N=617,453 *6 weeks*	PE, MSICS, or ECCE	0.5 mg in 0.1 mL of 0.5% MOX	No IC antibiotic	All patients	Endophthalmitis rate, TASS, adverse events
Haripriya, 2019[39]† *Retrospective Cohort*	N=2,062,643 *6 weeks*	PE, MSICS, or ECCE	0.5 mg in 0.1 mL of 0.5% MOX	No IC antibiotic	All patients	Endophthalmitis rate, corneal edema, TASS, adverse events
Herrinton, 2016[33] *Retrospective Cohort*	N=294,649 *3 months*	PE	0.25 mg MOX in 0.1 mL	No IC antibiotic or IC Cefuroxime	Varied	Endophthalmitis rate, macular edema, adverse events
Lane, 2008[46] *RCT*	N=57 *3 months*	PE	0.25 mg in 0.05 mL of undiluted 0.5% MOX	Salt solution injection	All patients	Corneal edema, TASS, adverse events
Matsuura, 2013[47] *Retrospective Cohort*	N=34,755 *1 month*	PE	Varied among institutions (0.05 mg/mL to 0.5 mg/mL MOX)	No IC antibiotic	NR	Endophthalmitis rate, TASS, adverse events
Matsuura, 2014[48] *Retrospective Cohort*	N=138 *3 months*	PE	0.15 mg/mL to 0.5 mg/mL of 0.5% MOX	Salt solution irrigation	All patients	TASS, adverse events
Melega, 2019[40] *RCT*	N=3,640 *6 weeks*	PE	0.15 mg in 0.03 mL of undiluted 0.5% MOX	No IC antibiotic	All patients	Endophthalmitis rate, adverse events
Porwal, 2021[35]† *Retrospective Cohort*	N=40,392 *NR*	MSICS	NR	No IC antibiotic	NR	Endophthalmitis rate
Rathi, 2021[36]† *Prospective Cohort*	N=42,466 *11 weeks*	PE or MSICS	0.1 mL of 0.5% MOX	IC Cefuroxime	Varied	Endophthalmitis rate, corneal edema, TASS, adverse events
Shenoy, 2021[41]†	N=214,782 *6 months*	PE or MSICS	0.1 mL of 0.5% MOX	No IC antibiotic	All patients	Endophthalmitis rate

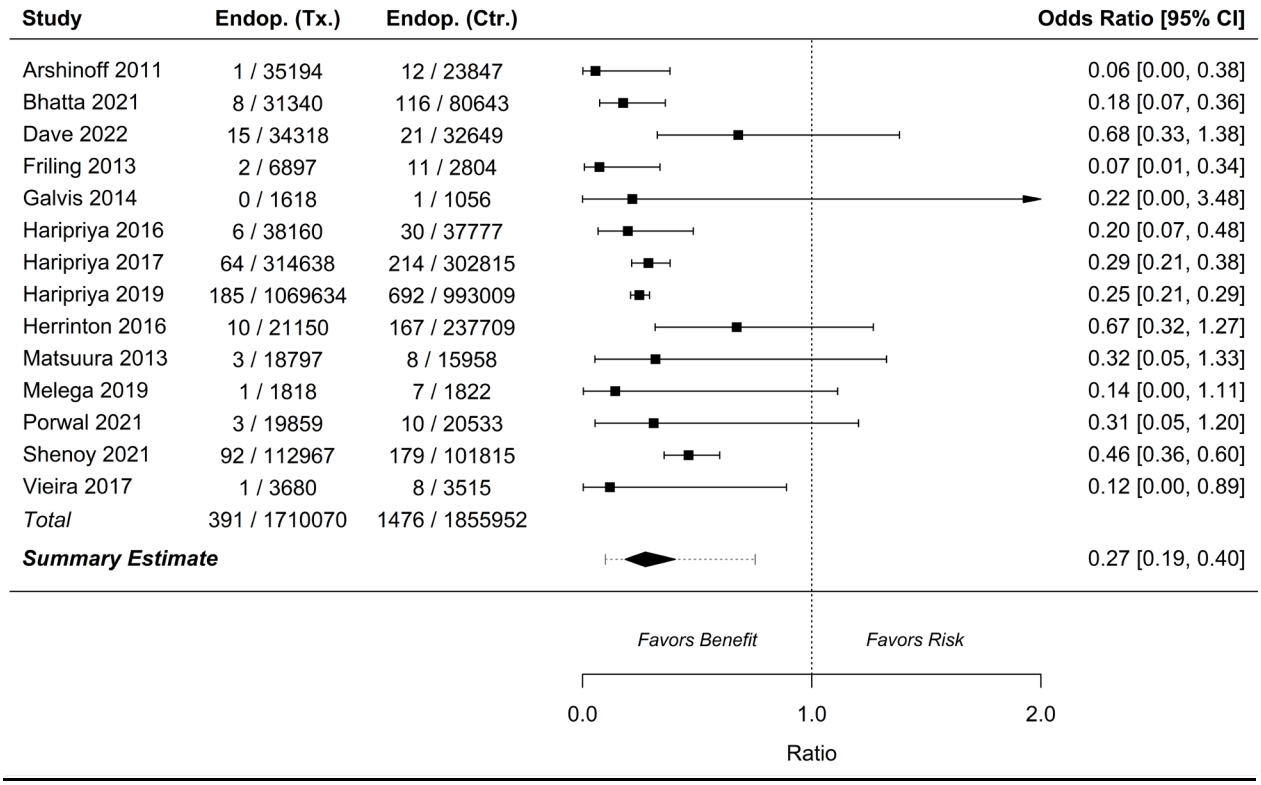
Study ***Study design***	**Sample Size** ***Follow-up***	**Surgery Type**	**Moxifloxacin Concentration and Preparation**	**Comparator**	**Topical Antibiotic Use***	**Outcomes Assessed**
Retrospective Cohort						
Shorstein, 2021[42]† *Retrospective Cohort*	N=204,655 *3 months*	NR	0.1 mL - 1 mL of 0.1% MOX	IC Cefuroxime	Varied	Endophthalmitis rate
Viera, 2017[43] *Retrospective Cohort*	N=7,195 *6 weeks*	PE	0.05 mL of MOX-hydrochloride at 5.45 mg/mL	No IC antibiotic	All patients	Endophthalmitis rate
Zhou, 2016[44]† *Retrospective Cohort*	N=222 *1 month*	PE	0.5 mg in 0.1 mL of 0.5% MOX	Topical MOX	Control group only	Corneal edema, macular edema, adverse events

Notes. Sample size is the number of eyes reported in each study. *Postoperative topical antibiotic use classified as: all patients received topical antibiotics, only control patients received topical antibiotics, and topical antibiotic use varied among included patients (*ie*, at surgeon discretion). **"Other" surgery not specified in the study. †Study not included in previous systematic reviews Huang 2016, Bowen 2018, and/or Wang 2020.
Abbreviations. ECCE=Extracapsular cataract extraction; IC=Intracameral, mg=milligram; MOX=moxifloxacin; mL=milliliter; MSICS=Manual Small Incision cataract surgery; NR=Not reported; PE=Phacoemulsification; TASS=Toxic anterior segment syndrome.

INTRACAMERAL MOXIFLOXACIN TO PREVENT ENDOPHTHALMITIS

Pooling estimates from 1 RCT and 13 cohorts (N = 3,566,022 eyes; Figure 2) indicates that intracameral moxifloxacin use is associated with a 73% reduction in odds of endophthalmitis compared to standard care (OR = 0.27, 95% CI [0.19, 0.40], p < .0001), corresponding to approximately 7 fewer cases of endophthalmitis per 10,000 eyes (RD = -0.0007, 95% CI [-0.0009, -0.0004], p < .0001). This estimate did not meaningfully differ when removing 1 study for which a continuity correction was necessary (OR = 0.28, 95% CI [0.19, 0.41]) or when data were pooled using the Peto method (OR_{Peto} = 0.34, 95% CI [0.26, 0.45]). Heterogeneity was limited (95% PI [0.10, 0.75]), suggesting that future studies would likely find substantively similar results (*ie*, reduced occurrence of endophthalmitis with intracameral moxifloxacin use). Similar to the overall results, the 1 included RCT[40] reported significantly lower incidence of endophthalmitis within 6 weeks of surgery among patients receiving moxifloxacin (1 of 1,818 eyes [0.05%], compared to 7 of 1,822 eyes [0.38%] in the topical eyedrop-only group; p = .04).

Figure 2. Occurrence of Endophthalmitis After Intracameral Moxifloxacin or Standard Care



Notes. Odds ratio for Galvis 2014 calculated with 0.5 added to all counts. Gray bars around summary estimate (diamond) represent 95% prediction interval.
Abbreviations. CI=confidence interval; Ctr=control group; Endop=endophthalmitis; Tx=treatment group.

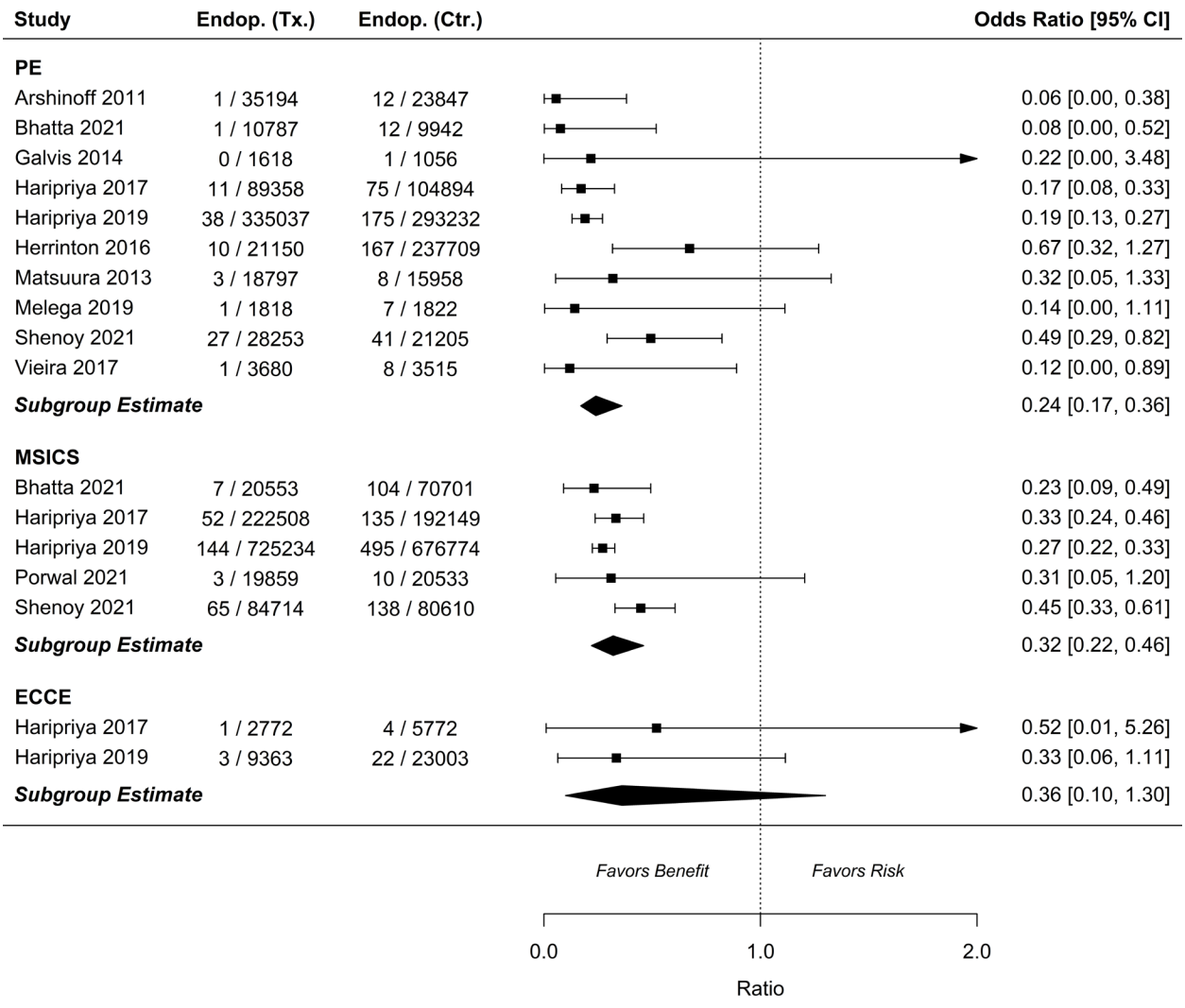
We also identified 2 small studies[45,48] (N = 203 eyes) that did not aim to assess the prophylactic benefit of intracameral moxifloxacin, but reported on occurrence of endophthalmitis among other adverse effects of cataract surgery. Both of these studies reported no instances of endophthalmitis among participants regardless of intracameral antibiotic use. Additionally, 5 studies[29,31,33,36,42] (N = 847,070 eyes) reported comparative effectiveness of intracameral moxifloxacin versus intracameral cefuroxime; when pooled, odds of endophthalmitis did not

significantly differ between antibiotic groups (OR = 1.34, 95 CI [0.73, 2.45], $p = 0.25$; OR_{Peto} = 1.34, 95% CI [0.84, 2.16]). Finally, odds of endophthalmitis after intracameral moxifloxacin or standard care did not appear to meaningfully differ by surgery type ($p = .54$; Figure 3).

Overall, we have moderate confidence in these findings as they are consistent, precise, and direct. The main limitation of the evidence is study design and methodological limitations of the studies, including lack of information on baseline patient and surgery characteristics, lack of adjustment for potential confounders, and unclear level and/or handling of missing data.

No studies specifically examined the effect of administration method (*eg*, diluted vs undiluted) or use of co-interventions (*eg*, with vs without topical antibiotic eye drops) on the efficacy of intracameral moxifloxacin.

Figure 3. Occurrence of Endophthalmitis After Intracameral Moxifloxacin or Standard Care by Surgery Type



Notes. Odds ratio for Galvis 2014 calculated with 0.5 added to all counts.
Abbreviations. CI=confidence interval; Ctr=control group; ECCE=extracapsular cataract extraction; Endop=endophthalmitis; MSICS=manual small incision cataract surgery; PE=phacoemulsification; Tx=treatment group.

ADVERSE EFFECTS OF MOXIFLOXACIN USE

Intracameral moxifloxacin use appears to be safe at the dosages and preparations reported, with few adverse events reported and none reported as directly related to intracameral antibiotic use. A single study[46] reported 2 cases of TASS with moxifloxacin use. The cases of TASS were discovered to be a part of a systemwide TASS epidemic (which included patients not enrolled in the study who did not receive intracameral moxifloxacin) due to use of reusable cannulas, which resolved after switching to disposable cannulas. Eight other studies[32,36-39,45,47,48] reporting TASS outcome reported no cases of TASS among included participants. No other adverse reactions to moxifloxacin were reported.

Several studies[30,33,34,36,39,44-46] reported on corneal or macular edema, which can occur as an adverse event of cataract surgery. No differences in these outcomes were reported between control patients and those receiving intracameral moxifloxacin, suggesting that use of intracameral moxifloxacin does not impact the rate of other potential adverse outcomes of cataract surgery.

DISCUSSION

Findings from this review indicate that intracameral moxifloxacin use is associated with a 73% reduction in odds of endophthalmitis compared to standard care (14 studies; OR = 0.27, 95% CI [0.19, 0.40], $p < .0001$). Given the low overall rate of postoperative endophthalmitis (0.08 to 0.14%), this corresponds to approximately 7 fewer cases of endophthalmitis per 10,000 eyes. Most studies utilized phacoemulsification cataract surgery, which is the preferred and most commonly performed type of cataract surgery.[49] However, in cases of more severe disease or limited access to equipment, extracapsular cataract extraction or manual small incision cataract surgery are still performed.[49,50] These types of surgery may have a higher risk for postoperative infection due to larger incisions and/or variation in manual surgical technique. However, in subgroup analyses, the reduction in odds of endophthalmitis after intracameral moxifloxacin did not appear to meaningfully differ by surgery type ($p = .54$), suggesting that intracameral moxifloxacin can be used across cataract surgery types.

When pooling the results of 5 studies[29,31,33,36,42] reporting comparative effectiveness of intracameral moxifloxacin versus intracameral cefuroxime, odds of endophthalmitis after cataract surgery did not differ by antibiotic type (OR = 1.34, 95 CI [0.73, 2.45], $p = 0.25$). While both moxifloxacin and cefuroxime appear to be effective at reducing rates of endophthalmitis, concerns around antibiotic resistance and potential adverse effects of cefuroxime have led to increased use of moxifloxacin as an alternative.[15] Although antibiotic resistance to moxifloxacin was not reported in any of the included studies, it should be considered as use of intracameral moxifloxacin expands.

Potential toxic effects of moxifloxacin have been reported at higher concentrations, with use of certain inactive ingredients in specific brands of moxifloxacin,[15] and with some compounded moxifloxacin.[18] However, none of the studies included in our review reported adverse events directly related to moxifloxacin use. A single study reported 2 cases of TASS, but these cases were determined to be a part of a hospital-wide outbreak stemming from the use of reusable cannulas.[46] Most included studies utilized the moxifloxacin brands Vigamox or Auromox, which do not have concerns around preservative use, pH, or compounding that have been linked to adverse events. Intracameral moxifloxacin use appears to be safe at the dosages and intracameral preparations reported in the included studies, but it is important to consider potential adverse effects with varying dosages, brands, or compounding of moxifloxacin.

Findings from this review align with those reported in previous reviews (reduced odds of endophthalmitis with intracameral moxifloxacin use: OR range 0.20 to 0.30),[14,16,17], even with the inclusion of 9 additional studies[34-39,41,42,44] not included in the previous systematic reviews. This consistency with previously reported findings suggests that these results may be unlikely to change with future research. However, limitations in the evidence base weaken our confidence in these findings.

LIMITATIONS

The main limitations of the evidence are study design and study methodology. Only 1 RCT[40] reported on endophthalmitis rates among the 21 included studies. The observational studies often compared surgeries before and after introduction of intracameral moxifloxacin as a standard for endophthalmitis prophylaxis within a hospital or health system. Although most studies were

done at a single center and/or by a single surgeon to minimize differences in surgery characteristics, the patient and/or surgery characteristics were often unreported and may have differed after introduction of intracameral moxifloxacin. A single study[33] adjusted for potential confounders between groups, and differences between moxifloxacin and control groups in the other studies may have biased the results. Additionally, no studies were conducted in the VHA and only 4 studies were conducted within the US. In the US, topical or injectable antibiotics must be used off-label for intracameral use, and this may confer additional risk of potential adverse events. Thus, current evidence may not fully capture the potential for adverse events in settings without access to commercially available intracameral moxifloxacin. Cataract surgery standards and procedures may also differ between countries and healthcare systems and the available evidence may not be fully applicable to cataract surgery care in the US or VHA.

Limitations of our review methods include use of a second reviewer check for study selection, data abstraction, and risk of bias assessment rather than dual independent review, and use of existing systematic reviews to identify literature prior to 2016. However, the likelihood of missing relevant studies is low as we utilized several existing systematic reviews with comprehensive searches.

FUTURE RESEARCH

Although existing research consistently shows prophylactic benefit of intracameral moxifloxacin, rigorous studies conducted in US settings may increase support for broader use of intracameral moxifloxacin in place of or alongside topical antibiotics. A triple blinded RCT[51] is currently underway in the US examining use of intracameral moxifloxacin compared to placebo, and findings from this study may improve our confidence in the existing evidence. This study and further RCTs conducted in the US may also increase the likelihood of FDA approval of intracameral moxifloxacin, enabling more standardized use of intracameral moxifloxacin across the US and within the VHA. Expanded use of intracameral moxifloxacin as a standard of care without FDA approval may increase risk and liability challenges. Finally, most studies included the use of topical antibiotics in both intervention and control groups, and direct comparison of intracameral moxifloxacin to topical antibiotics was limited to a single study.[44] Further studies directly comparing intracameral moxifloxacin alone to topical antibiotics are warranted.

CONSIDERATIONS FOR USE OF INTRACAMERAL MOXIFLOXACIN IN VHA

Within the VHA, limited access to intracameral antibiotics has led to irregular and inconsistent usage across VHA facilities. In a 2016 survey of VHA ophthalmology chiefs, 33% reported use of intracameral antibiotics during cataract surgery (23% cefuroxime, 50% moxifloxacin, 18% vancomycin).[52] Among those reporting no use of intracameral antibiotics, institutional and/or pharmacy difficulties was most often rated as the reason for non-use, followed by risk of dilution error, lack of evidence, risk of bacterial resistance, and risk of contamination.[52] Given the concerns around patient adherence and correct administration of topical eye drops, particularly among Veterans who may have barriers to compliance such as older age and higher rates of comorbidity and disability,[10,11] consistent policies and procedures for the use of intracameral antibiotics within the VHA are needed. However, variation in access to intracameral preparations of moxifloxacin across VHA sites creates challenges for consistent usage and concerns of increased risk from use of off-label compounded moxifloxacin. Availability of an FDA-approved

intracameral antibiotic or standardized in-house preparation of intracameral moxifloxacin by the VHA pharmacy may be needed to enable standardized use.

CONCLUSIONS

Intracameral moxifloxacin use is associated with substantially reduced odds of endophthalmitis compared to standard care. Additionally, intracameral moxifloxacin appears to be safe at the dosages and preparations reported in the included studies, with no reported adverse events related to moxifloxacin use. Available evidence may not be fully applicable to US or VHA healthcare settings, however, and future research with improved methodology and in US settings is warranted to inform standardized use of intracameral moxifloxacin within the VHA. Consistent usage of intracameral moxifloxacin across VHA sites is dependent upon consistent policies, procedures, and access to standardized intracameral preparations of moxifloxacin for intracameral use.

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