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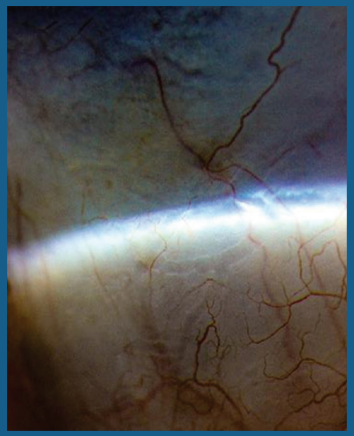

Prominent lymphatic vessel

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- To provide a platform for the publication of information with a focus on Ophthalmology in Asia.
- To disseminate information that will improve the care of patients with all types of ophthalmological disorders, with a special focus on glaucoma.
- To increase the understanding of such disorders through reporting of educational activities.
- To publish the results of research programmes to expand knowledge about the causes, prevention, and treatment of ophthalmological disorders.
- To work closely with Asian and international researchers to achieve these aims.
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Although the focus of Asian Journal of Ophthalmology mainly was on glaucoma with close ties to the South-East Asian Glaucoma Interest Group (SEAGIG) in the past, the journal now focuses on the entire spectrum of Ophthalmology.

Asian Journal of Ophthalmology and Kugler Publications have started to collaborate since mid 2012 on the publication of the journal. A new website has been launched (www.asianjo.com), which facilitates all aspects of the peer-review and publication process, from manuscript submission to publication.

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The Asia-Pacific Glaucoma Congress 2021 Abstract Book is available as a supplement on our website.

Asian J Ophthalmol. 2021;18:4-6

Editorial
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Is indiscriminate use of intracameral route for prophylactic antibiotics in cataract surgery appropriate?

As doctors, we do what we think is best for our patients. We make decisions to benefit our patients. It is preferable that these decisions were not influenced by costs, profit, or obedience to the medico-legal system.

The use of intracameral route for prophylactic antibiotics in cataract surgery was initially proposed for facilities with a high incidence of endophthalmitis. Subsequent studies in situations where there was a high incidence of endophthalmitis were interpreted to show that it was beneficial in reducing the incidence of endophthalmitis. It subsequently became the recommendation for everyone whether they experience a high incidence of endophthalmitis or not. Upon becoming a recommendation, its use became more widespread, even by those who felt it was not necessary. The medico-legal system then perpetuated the indiscriminate use of the intracameral route for prophylactic antibiotics by suggesting that not using it would be substandard care.

In this issue, "Incidence of post-cataract surgery endophthalmitis: a chronological review and intercontinental comparison" by Wen *et al.* reviews the historical aspect of endophthalmitis in cataract surgery. The review found that some studies which showed a marked improvement in incidence of endophthalmitis had a higher-than-average baseline endophthalmitis rate. The worldwide incidence of endophthalmitis has been lower in recent years. In some countries, such as Japan in which the use of intracameral antibiotics is estimated at 11.8%, the incidence of endophthalmitis is 0.025%, which is lower than in countries where intracameral antibiotics are used routinely.[1]

The volume of the anterior chamber is about 0.24 ml or 240 µL. Given that aqueous inflow is approximately 2.4 µL per minute, the total volume of aqueous in the anterior chamber is replaced every 100 minutes. In 100 minutes, the concentration of antibiotic would be half, and in 200 minutes, it would be a quarter. Hence, in 3.5 hours, the concentration of antibiotic would be a quarter, possibly falling below the minimal inhibitory concentration. Therefore, logically, prophylactic intracameral antibiotics would only be effective in preventing infections due to bacteria that entered the eye during cataract surgery.

By contrast, subconjunctival or topical antibiotics should maintain the ocular surface and adnexa sterile, thus inhibiting bacterial entry postoperatively. Subconjunctival antibiotics often ooze through the needle injection site and so would function to bathe the ocular surface with antibiotics.

In a surgical facility with high standards of sterility, there is little chance of bacteria being introduced intraoperatively. However, when cataract surgery is done in makeshift camps or settings with lower standards of sterility, bacterial inoculation is possible; these are the contexts where intracameral antibiotics may be needed. On the other hand, if the eye and eyelids have been prepped with povidone-iodine, the lids have been excluded from the incisions, and the instruments are sterile, it is likely that no bacteria would enter the eye.

Intracameral antibiotics can be useful when wounds are compromised or surgery is prolonged due to complications. In cases of wound compromise, bacteria can enter the eye for 24 hours or more, so the risk of endophthalmitis can persist for 24 hours postoperatively. Therefore, in these cases subconjunctival and topical antibiotics would be more useful.

In general, routine uncomplicated cataract surgery done by an experienced surgeon on a healthy patient with good hygiene in a surgical facility with high standards of sterility should carry negligible risk of endophthalmitis. In such cases, it would be adequate to use subconjunctival or topical antibiotics and not expose the patient to the risk of intracameral antibiotics. However, if a surgical facility has suboptimal standards of sterilization, the surgeon lacks experience, there are surgical complications, or the patient has poor hygiene with associated inflammation of ocular adnexa, the use of intracameral antibiotics is warranted.

Is there a significant difference in postoperative endophthalmitis rates between intracameral and subconjunctival antibiotics when cataract surgery is performed by experienced surgeons in facilities with high standards of sterility? This is the question posed by Lim *et al.* in a brief report titled, "Is zero incidence of endophthalmitis after cataract surgery achievable?", also included in this issue.

Ironically, many of the proponents of intracameral antibiotics are experienced surgeons and would realize that their low rates of endophthalmitis are actually due to their sound surgical skills and settings should they audit their own results. Instead, their good results are automatically attributed to the routine use of intracameral antibiotics based on previously published studies and medico-legal recommendations.

The risk of significant adverse reaction to prophylactic antibiotics is greater with the intracameral route than subconjunctival and topical routes. "Subconjunctival antibiotics: an alternative to intracameral antibiotics for endophthalmitis prophylaxis in cataract surgery" by Xuan *et al.* evaluates subconjunctival and intracameral antibiotics in this issue. Subconjunctival antibiotics can maintain bactericidal levels in the anterior chamber for up to 12 hours compared to intracameral antibiotics, which have a four-fold reduction in concentration within an hour.

Serious complications associated with intracameral antibiotics, which can be even more devastating than postoperative endophthalmitis, include retinal

detachment, retinal infarction, vancomycin related hemorrhagic occlusive retinal vasculitis, cefazolin-associated retinal toxicity, and toxic anterior segment syndrome. There are no significant adverse effects associated with subconjunctival cephalosporins; the only theoretical risk could be inadvertent penetration of the eye by the hypodermic needle during injection.

Hence, in low-risk settings, it may be preferable to consider the subconjunctival and topical routes, which have a higher safety margin. In the reprint article "Intracameral antibiotics debate" originally published in Eurotimes in the May 2020 issue, Professor Antoine Brézin indicated that his use of intracameral antibiotics in cataract surgery is not due to scientific reasons, but rather because of official recommendation and medico-legal concerns.

There is understandable concern around legal liability for not using intracameral antibiotics if a patient develops endophthalmitis after cataract surgery. However, equally concerning is the possibility of legal liability if a patient suffers an adverse reaction to intracamerally administered prophylactic antibiotics when safer subconjunctival and topical routes are available.

Surgeons should be wise in their choice of route for prophylactic antibiotics and consider the risks and benefits in different situations. With the improvement of cataract surgery techniques and instrumentation to date as well as attention to wound construction and closure, indiscriminate routine use of the intracameral route for prophylactic antibiotics in cataract surgery, which is largely encouraged by the medico-legal system, may not be appropriate if risks outweigh the benefits.

Keith Ong
Chief Editor
Asian Journal of Ophthalmology

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Intracameral antibiotics debate

Modern surgery raises new questions regarding the use of intracameral antibiotics*

In this age of modern cataract surgery with improved surgery and sterile techniques, is the use of intracameral antibiotics still necessary to reduce the incidence of endophthalmitis? That was the question addressed in a debate held at the 37th Congress of the ESCRS in Paris, France.

Arguing in favour of intracameral antibiotics was one of the early proponents of the practice, Prof Anders Behndig MD, PhD, Umeå University Hospital, Umeå, Sweden.

"I have been a cataract surgeon since 1993. I've used intracameral antibiotics in every single case since 1999 and I wouldn't dare to do anything else," Prof Behndig said.

He pointed out that in the 15 years since the publication of the ESCRS endophthalmitis prophylaxis study, decreased rates of postoperative endophthalmitis (POE) have accompanied the adoption of intracameral antibiotics by ophthalmic surgery practices around the world.

He noted that Swedish cataract surgeons had already adopted intracameral cefuroxime because the Swedish National Cataract Register (NCR) – which has registered endophthalmitis after cataract surgery (POE) since 1998 – showed that intraocular antibiotics such as cefuroxime, moxifloxacin and ampicillin can significantly reduce the POE rate.

The reports from the Swedish NCR were the inspiration behind the ESCRS endophthalmitis study, he noted. The prospective randomised controlled trial involved 16,603 cataract patients who underwent cataract surgery at 24 centres throughout Europe from September 2003 to January 2006. It showed that the POE rate among patients randomised to receive intracameral cefuroxime was only 0.03% in those who also received levofloxacin drops, and only 0.05% in those who received placebo drops. That compared to POE rates of 0.17% and

*This article is reprinted with the permission of ESCRS EuroTimes, official news magazine of the European Society of Cataract and Refractive Surgeons.
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Posted: Friday, May 1, 2020

0.25% in the same respective groups who did not receive the intracameral antibiotic.

Since that time, the near universal adoption of intracameral antibiotics in France has coincided with a reduction in the incidence of POE from 0.145% in 2005 to 0.044% in 2014 (Creuzot-Garcher C, *et al.* Ophthalmology. 2016;123:1414-20). In a very recent study from India, a review of 2,062,643 cataract surgeries showed that the rate of POE was only 0.02% in patients that received intracameral moxifloxacin compared to 0.07% in those who did not receive it (A Haripriya *et al,* J Cataract Refract Surg. 2019 Jul 29. [Epub ahead of print]).

"Intracameral antibiotics have been used in many millions of cataract procedures and they reduce endophthalmitis rates by three- to seven-fold in different studies and side-effects are extremely rare," Dr Behndig added.

The fear factor

Prof Antoine Brézin MD, Université Paris Descartes, Paris, France, maintained that intraocular antibiotics should not be mandatory in cataract surgeries, as in France where there is now an official recommendation in favour of the prophylaxis approach.

"Doubtless the incidence of endophthalmitis after cataract surgery has gone down dramatically over the past 15 years, but is it really due to the use of intracameral antibiotics? I think we have been brainwashed to believe it is cefuroxime, but I think there are a number of other factors to consider," he said.

He argued that although the ESCRS study showed that intracameral cefuroxime reduced the rates of POE, it also confirmed that surgical complications were a major risk factor for POE. Other studies have shown rates of POE after cataract surgery without intracameral antibiotics as low as those achieved with them in the ESCRS study. He cited a Japanese study that showed that among 63,244 cataract patients the rate of POE was only 0.025%, even though only 11.8% received intracameral antibiotics *(T Inoue et al Jpn J Ophthalmol 2018; 62:24-30)*.

Other surgical factors may therefore may play a more important role in preventing the complication. He noted, for example, in the ESCRS study the risk of the POE was more greatly elevated by the use of clear corneal incisions instead of scleral tunnel incisions than it was by the absence of intracameral antibiotics (5.8-fold vs 4.9-fold), Dr Brézin said.

Prof Brézin added that the studies cited in support of the ESCRS study are almost all based on before-and-after comparisons, which overlook the many advances in cataract surgery that may have also contributed to the reduction of the complication. Such advances include smaller incisions that are less prone to leakage, shorter surgical times and fewer complications like posterior capsule rupture. Other factors include improved surgical theatre air filtration and pre-loaded IOL cartridges.

He noted that a study prospectively comparing the outcome of cataract surgery with and without intracameral antibiotics in 15,000 cataract patients showed that the prophylaxis did not significantly reduce the incidence of POE (0.108% vs 0.15%, p=0.57) *(Sharma et al, J Cataract Refract Surg. 2015;41:393-399)*.

"In 2019, do I inject because of the science? No, I inject because of the official recommendation. I inject because of the fear factor, because, like everyone else, I'm afraid of lawyers. But if we could turn the page back, I think I would no longer do so," Prof Brézin concluded.

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5th Asia-Pacific Glaucoma Congress

The 5th Asia-Pacific Glaucoma Congress (APCG) was held virtually for the first time from 4–8 June 2021, hosted by the Asia-Pacific Glaucoma Society. The Asia-Pacific Glaucoma Congress brought together clinicians, scientists, students, and other health practitioners from the Ophthalmology field with a focus on Glaucoma. The program provided a platform for delegates to collaborate, share experiences, knowledge and research results whilst also learning about world's best practice and the recent innovations helping us overcome challenges in clinical medicine and surgery.

The APGC invited submissions for the official program over a broad range of themes, including but not limited to, basic research and pathogenesis, epidemiology and economic evaluation, glaucoma imaging and diagnosis, glaucoma surgery, laser treatment and medical treatment. Over 220 abstract submissions were received and peer reviewed to ensure a fair and equitable process. Accepted into the official program were 98 poster presentations and 41 on-demand oral presentations, including 8 highlighted oral presentations which will participate in the "best free papers" session in the live scheduled program.

The APGC Abstract Book is included as a supplement to this issue of Asian Journal of Ophthalmology

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Brief Report
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Is zero incidence of postoperative endophthalmitis after cataract surgery achievable?

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Abstract

Purpose: *For over 10 years, there have been zero cases of postoperative endophthalmitis (POE) after cataract surgery at Chatswood Private Hospital (CPH), Sydney, Australia.*

Study design: *We conducted a retrospective audit study to evaluate the reasons for this, as well as the different preferences for route of antibiotic prophylaxis used.*

Methods: *Deidentified data on cataract surgery cases for 2010–2020 were extracted and analyzed descriptively.*

Results: *A total of 28,937 cataract surgery cases were performed at CPH from 2010-2020, for which no cases of POE were identified. The intracameral route for antibiotic prophylaxis was more commonly used compared to subconjunctival or both.*

Conclusion: *Administration of prophylactic antibiotics, regardless of the route of administration, is beneficial and equally effective in preventing POE. Having operating theatres dedicated to ophthalmology helps maintain high standards of sterility of instrumentation and operating environments.*

Keywords: *cataract surgery, endophthalmitis, prophylactic antibiotics*

Introduction

Postoperative endophthalmitis (POE) is a rare but severe vision-threatening complication that can arise following cataract surgery.[1] The incidence has been reported to be between 0.13% and 0.7% in the literature.[2] More recent papers have quoted rates to be as low as 0.1%.[3]

There have been no cases of POE after cataract surgery for over 10 years at Chatswood Private Hospital (CPH) in Sydney, Australia and its predecessor facility, Ophthalmic Surgery Centre (North Shore). Electronic records data from 2010 to 2020 were analyzed.

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A retrospective audit study was performed to evaluate the reasons for the good results at CPH. As surgeons have different preferences for route of antibiotic prophylaxis, this was also analyzed.

Methods

Cataract surgery cases were defined in this study as procedures with Australian Medicare item number 42702, under the description of cataract extraction and insertion of intraocular lens implant. Combined cases of cataract surgery with glaucoma surgery, corneal grafting, and vitreoretinal surgeries were excluded.

Deidentified data on cataract surgery cases was extracted from records of CPH via computer software for the years 2010–2020. This included data on the different routes of prophylactic antibiotic administration (intracameral, subconjunctival, or both) as well as the total number of cataract cases performed over the years. Descriptive statistics were used to analyze the data.

Results

From 2010 to 2020 (11 years), a total of 28,937 cataract cases were performed at CPH, of which there were no cases of POE.

Data of the breakdown of the different routes of prophylactic antibiotic administration was only available for the year 2013 and from 2016–2020, as shown in Table 1. The various routes of antibiotic administration included intracameral, subconjunctival, or both. Cephazolin and cefuroxime (0.1 ml of 10 mg/ml) were the intracameral antibiotics used. Cephazolin and cephalothin (0.2 to 0.5 ml of 100 mg/ml) were the subconjunctival antibiotics used.

In 2013, intracameral antibiotics were more widely used, proportions being 60% for intracameral, 26% for subconjunctival, and 14% for both intracameral and subconjunctival antibiotics. This trend continued over the past 5 years (2016–2020), with intracameral antibiotics remaining the more common route of

Table 1. Routes of prophylactic antibiotic administration at Chastwood Private Hospital 2016–2020

Year	Intracameral (%)	Subconjunctival (%)	Both subconjunctival / Intracameral (%)	Total
2016	2,073 (85)	269 (11)	94 (4)	2,436
2017	2,236 (82)	355 (13)	136 (5)	2,727
2018	3,171 (88)	379 (11)	44 (1)	3,594
2019	3,556 (84)	624 (15)	68 (2)	4,248
2020	3,928 (86)	456 (10)	165 (4)	4,549

antibiotic administration at an average proportion of 85%, followed by subconjunctival antibiotics (12%), and both (3%). Furthermore, the use of intracameral route for antibiotic prophylaxis after cataract surgery had increased over the years at CPH (Figs. 1–3).

There being no cases of POE after cataract surgery meant that besides the different routes of antibiotic administration, there may be other factors that contribute to lack of POE cases at CPH.

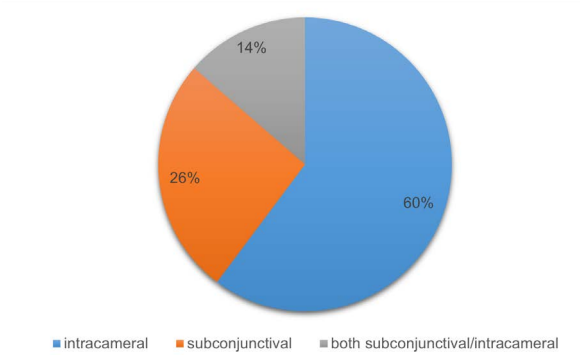

Fig.1. Route of prophylactic antibiotic administration at Chastwood Private Hospital in 2013.

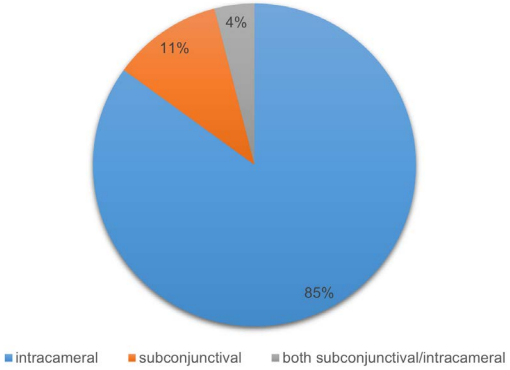

Fig. 2. Route of prophylactic antibiotic administration at Chastwood Private Hospital in 2016.

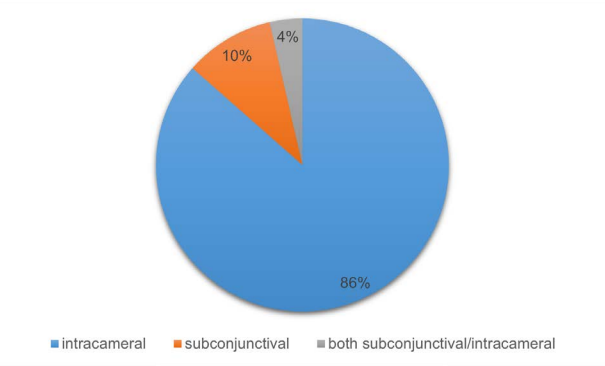

Fig. 3. Route of prophylactic antibiotic administration at Chastwood Private Hospital in 2020.

Discussion

A total of 28,937 routine cataract surgery cases were performed at CPH from 2010 to 2020, of which no cases of POE were recorded. The lowest rate of POE in the literature was quoted to be 0.01%, which would have equated to 2.89 cases at this facility. It would be useful to discuss possible reasons behind the low incidence of POE at CPH.

The causes of POE are manifold and can be divided into endogenous, intraoperative, and postoperative factors. Bacteria from the patient's own ocular surface or adnexa is most often the primary source of infection, with gram-positive, coagulase-negative cocci (*Staphylococcus epidermidis*) accounting for most culture positive cases.[4] Endogenous causes include debilitated or immunocompromised patients with bacteremia or fungemia, which is unlikely in the scenario of elective cataract surgery. Intraoperative inoculation of bacteria can occur as a result of suboptimal operating environments and sterility of instrumentation, as well as inadequate preparation of surgical sites with antiseptic or surgical drapes. Infected eyelid adnexa can lead to endophthalmitis both intra and postoperatively. On the other hand, suboptimal wound closure can result in leakage of aqueous and tear entry into the eye postoperatively.[4] This presents a route for bacteria present in the tear film or eyelid adnexa to enter the eye, resulting in POE.

One of the reasons that may contribute to the low incidence of endophthalmitis at CPH is having operating theatres dedicated to ophthalmology, with high levels of sterility that prevent intraoperative inoculation of bacteria. Meticulous preparation of the patient with application of topical povidone-iodine also significantly reduces the likelihood of infection.[1,4,5]

Furthermore, the results obtained from the retrospective audit study suggest that prophylactic antibiotics, whether administered through an intracameral or subconjunctival route are equally effective in preventing POE. Theoretically, intracameral antibiotics would be more useful in settings where there is intraoperative inoculation of bacteria, for example, in resource-poor settings where high levels of sterility in operating theatres is less feasible. On the other hand, subconjunctival antibiotics, which often ooze through the needle injection site, would function to bathe the ocular surface with antibiotics.[6] This might prove more useful in keeping the ocular surface and adnexa sterile, hence preventing bacteria from entering the eye postoperatively.

Other preventive strategies would involve identifying and managing the suboptimal conditions that could potentially lead to POE, as discussed above. From a surgical perspective, wounds with a long intracorneal track are more secure and conducive for wound apposition. Suturing wounds that are insecure would add another layer of protection and security. Should any concerns regarding intra- and postoperative inoculation of bacteria arise, consideration should be given for use of both intracameral and subconjunctival antibiotics for synergistic effect. Finally, elective cataract surgery should be postponed if concerns of infected adnexa are present.

Conclusion

This study shows that a low or zero incidence of POE after cataract surgery is achievable. Meticulous wound construction, attention to detail pre-, intra-, and postoperatively, and taking appropriate measures as necessary contribute to the prevention of POE. Having operating theatres dedicated to ophthalmology helps maintain high standards of sterility of instrumentation and operating environments. This study also provides evidence that administration of prophylactic antibiotics, regardless of the route of administration, is beneficial and equally effective in preventing POE.

Declarations

Ethics approval and consent to participate

Not required.

Consent for publication

Not required

Competing interests

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Review Article
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Incidence of post-cataract surgery endophthalmitis: a chronological review and intercontinental comparison

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Abstract

Purpose: *This review aimed to investigate the global incidence of postoperative endophthalmitis (POE) after cataract surgery over the last three decades, with a particular focus on the use of prophylactic intracameral antibiotics.*

Study design: *Literature review.*

Methods: *A literature search was performed in PubMed and Scopus. Data was collected from included studies and analyzed in IBM SPSS v27.*

Results: *A total of 63 studies from 20 regions were included. The use of prophylactic intracameral antibiotics significantly reduced POE incidence. The baseline POE incidence in studies that involved intracameral prophylaxis tended to be high. A downward linear trend in POE incidence was observed in studies that did not involve intracameral antibiotic prophylaxis. Interestingly, a study in Japan reported the use of intracameral antibiotic prophylaxis in only 10.4% of cataract surgeries with an overall POE incidence of 0.025%, which is comparable to countries that use intracameral prophylaxis routinely. Within studies from Australia, China, Europe, India, Singapore and United States, Australia had the highest POE incidence with and without intracameral prophylaxis, while China had the lowest POE incidences.*

Conclusion: *Intracameral antibiotics are an effective prophylaxis against POE. However, the incidence of POE is decreasing worldwide even without intracameral prophylaxis. The benefits of intracameral antibiotics should be weighed against its risks prior to its implementation as routine prophylaxis protocol for cataract surgery.*

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

Introduction

A rare, but serious complication of cataract surgery is endophthalmitis. Postoperative endophthalmitis (POE) after cataract surgery has been reported to affect up to 0.5% of patients[1] and can be extremely debilitating to the affected

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individuals. Symptoms include ocular pain, red eye, and decreased vision.[2] Treatment regimens are invasive and include specimen collection via vitreous tap/biopsy or vitrectomy and intraocular antibiotic administration. Visual prognosis remains poor despite treatment, with only 40–57% of patients achieving a visual acuity equivalent to ≥ 6/12.[3]

A 2005 review looking at the incidence of POE worldwide reported an increase from 1992–2003 despite advances in cataract surgery techniques.[4] It was postulated that the increased incidence could be attributed to the new technique of phacoemulsification and the transition from scleral tunnels to clear corneal incisions. There is therefore a clear interest in minimizing POE complication rates, with an increasing focus on the role of prophylactic antibiotics. To our knowledge, this is the most recent meta-analysis to assess trends in POE incidence across multiple countries.

In 2007, the European Society of Cataract and Refractive Surgeons (ESCRS) published the Endophthalmitis Study, showing a five-fold decrease in POE when intracameral (IC) cefuroxime was used prophylactically at the end of the surgery.[5] Prior to this study, prophylactic regimens for cataract surgeries typically involved ensuring a sterile surgical environment with the use of povidone-iodine ± topical/subconjunctival antibiotics. The use of IC antibiotics as part of routine prophylaxis has since been recommended in the ESCRS guidelines,[1] and several systematic reviews have established a significantly reduced risk of POE with IC antibiotics.[6–8]

However, the administration of IC antibiotics has been associated with increased risks of toxic anterior segment syndrome, retinal pathology, and endothelial toxicity.[9,10] Despite the ESCRS recommendations, there is still no single approach to POE prophylaxis worldwide. While Swedish and French ophthalmologists routinely use intracameral antibiotics,[11] only 50% of US ophthalmologists and 30% of Canadian ophthalmologists use these as prophylaxis. In Japan, topical antibiotics are preferred, with only 7% of ophthalmologists adopting the use of IC antibiotics.[12]

Although the benefits of IC antibiotics are evident, the associated risks are severe, and the benefit-risk ratio should be carefully considered for each patient. To facilitate this consideration, it is imperative to understand the natural historical aspect of POE incidence: has the incidence of POE continued to increase or has it decreased? This review therefore aims to investigate the trends in POE incidence worldwide over the past three decades. We hypothesize that with improving surgical and aseptic techniques, POE incidence has decreased even outside the context of prophylactic IC antibiotics.

Methods

Literature search

A literature search was carried out in PubMed and Scopus using a predefined search strategy (Table 1). Relevant papers identified through references were also included in the review. Abstracts were screened according to the inclusion and exclusion criteria, following which full-text articles were obtained to further assess eligibility. Studies were included if they were English articles published between 2000 and 2021, if they were a randomized controlled trial or a retrospective/prospective cohort study (this included clinical registries, chart reviews, etc.), if the subjects were humans, and if they reported POE incidence as one of their primary outcomes. Studies were excluded if they included less than 1,000 eyes, if they focused on subset populations (*e.g.*, patients with pre-existing risk factors for POE or pediatric populations), if the study focused on modified cataract surgeries

Table 1. Search terms and filters used in PubMed and Scopus

Search strategy	
Database	**Keywords and MeSH terms**
PubMed	((endophthalmitis*[tiab] OR Endophthalmitis [MeSH]) AND (cataract extraction* OR Cataract Extraction [MeSH]cataract extraction* OR Cataract Extraction [MeSH] OR Lens Implantation, Intraocular [MeSH])) AND (("2000/01/01"[Date - Publication]: "3000"[Date - Publication]))
	Filters applied: Abstract, Full text, Clinical Study, Clinical Trial, Comparative Study, Controlled Clinical Trial, Evaluation Study, Government Publication, Multicenter Study, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial, Validation Study, Humans, English.
Scopus	((TITLE-ABS-KEY(cataract surgery OR cataract extraction OR phacoemulsification)) AND (TITLE-ABS-KEY(endophthalmitis))) AND (retrospective study OR prospective study OR randomised* trial) AND (LIMIT-TO (SRCTYPE,"j")) AND (LIMIT-TO (DOCTYPE,"ar")) AND (LIMIT-TO (PUBYEAR,2021) OR LIMIT-TO (PUBYEAR,2020) OR LIMIT-TO (PUBYEAR,2019) OR LIMIT-TO (PUBYEAR,2018) OR LIMIT-TO (PUBYEAR,2017) OR LIMIT-TO (PUBYEAR,2016) OR LIMIT-TO (PUBYEAR,2015) OR LIMIT-TO (PUBYEAR,2014) OR LIMIT-TO (PUBYEAR,2013) OR LIMIT-TO (PUBYEAR,2012) OR LIMIT-TO (PUBYEAR,2011) OR LIMIT-TO (PUBYEAR,2010) OR LIMIT-TO (PUBYEAR,2009) OR LIMIT-TO (PUBYEAR,2008) OR LIMIT-TO (PUBYEAR,2007) OR LIMIT-TO (PUBYEAR,2006) OR LIMIT-TO (PUBYEAR,2005) OR LIMIT-TO (PUBYEAR,2004) OR LIMIT-TO (PUBYEAR,2003) OR LIMIT-TO (PUBYEAR,2002) OR LIMIT-TO (PUBYEAR,2001) OR LIMIT-TO (PUBYEAR,2000)) AND (LIMIT-TO (LANGUAGE,"English"))

(*e.g.*, immediately sequential bilateral cataract extraction or cataract surgeries combined with other ophthalmological procedures), if the study did not mention the use or non-use of any prophylactic measures against POE, and if the POE incidence was not reported in absolute figures.

Data collation

Data from each study was extracted and compiled in standardized form including: (a) year of publication, (b) country/region, (c) study type, (d) study period, and (e) reported POE incidence in percentage and absolute figures.

Where reported, any prophylactic measure, *i.e.*, IC antibiotics and the corresponding POE incidence (in percentage and absolute figures) was also recorded. In studies that reported the incidence of both presumed POE (diagnosed clinically) and culture-positive POE, the presumed POE incidence was recorded. In studies that reported endophthalmitis complication rates for procedures other than cataract surgeries, only the relevant data (POE following cataract surgery) was recorded. In studies that only provided absolute figures, percentages were calculated.

Statistical analysis

All analysis was performed in IBM SPSS Statistics v.27. Some of the included studies reported POE incidence over a few years, *i.e.*, x% between 2001 and 2005. For these studies, we identified the median year and generated a scatter plot of overall POE incidence (%) against year.

Studies were separated into those that included prophylactic IC antibiotics and those that did not. Within these groups, studies were further separated into studies that only had single data points and studies with multiple data points. Binary logistic regression was performed on the following groups: (A) all studies that involved prophylactic IC antibiotics, (B) all studies that did not involve IC antibiotics, and (C) studies that only had single data points. If a study including IC antibiotics did not provide absolute figures for the breakdown of POE cases in non-IC antibiotic groups *versus* IC antibiotic groups, they were excluded from this analysis.

For group A, a generalized estimating equation with study ID as subject identifier, an exchangeable correlation structure (robust estimator) and a logit link function was used to investigate the effects of prophylactic IC antibiotics on POE incidence. For group B, a generalized estimating equation with study ID as the subject identifier, year fitted as a within subject covariate with an AR(1) autoregressive correlation structure (robust estimator), and a logit link function was used to investigate any time trends associated with POE incidence. For group C, a generalized linear model with a logit link function was used to investigate if there were any time trends associated with POE incidence in this group. Line plots for

groups A and B, and a scatter plot for group C were also generated. Results were considered significant if $p < 0.05$.

Studies from Australia, China, Europe, India, Singapore, and United States were identified, and the pooled POE incidence for each region was calculated to generate a bar chart. These pooled incidence rates were further categorized into POE incidence for patients who did not receive prophylactic IC antibiotics and patients who received IC antibiotics.

Results

Study characteristics

A total of 63 studies were included in our analysis (Table 2). These studies consisted of: eight studies from India,[13–20] eight from Spain,[21–28] eight from United States,[29–36] six from United Kingdom,[37–42] five from Sweden,[43–47] four from Brazil,[48–51] four from Japan,[52–55] three from France,[56–58] two from China,[59,60] two from Greece,[61,62] two from Ireland,[63,64] two from Singapore,[65,66] and a single study each from Australia,[67] Canada,[68] Europe,[5] Germany,[69] Hong Kong,[70] Israel,[71] Portugal,[72] Saudi Arabia,[73] and Taiwan.[74] Thirty-one of these studies included the use of prophylactic IC antibiotics. One study was excluded from the subgroup analysis as it did not report the breakdown of POE cases within groups receiving and not receiving IC antibiotics.[56] Within the remaining thirty, three studies had a single data point. Twenty-seven studies included data points from patients not receiving IC antibiotics; for the purpose of this review, we shall refer to these patients as the 'baseline' groups within those studies.

Table 2. Characteristics of included studies

Study ID	Year	Authors	Country/ region	Study type	Reference
1	2019	Moser *et al.*	Spain	Retrospective observational study	21
2	2019	Haripriya *et al.*	India	Retrospective multicenter clinical registry	13
3	2019	Melega *et al.*	Brazil	Prospective randomized partially masked single-site clinical trial	51
4	2018	Tuñí-Picado *et al.*	Spain	Retrospective comparative study	22

Study ID	Year	Authors	Country/ region	Study type	Reference
5	2018	Inoue *et al.*	Japan	Prospective multi-center study	52
6	2017	Haripriya *et al.*	India	Retrospective clinical registry	14
7	2016	Haripriya *et al.*	India	Retrospective clinical registry	15
8	2016	Herrinton *et al.*	US	Observational, longitudinal cohort study	29
9	2015	Katz *et al.*	Israel	Retrospective consecutive cohort study	71
10	2015	Sharma *et al.*	India	Prospective comparative interventional cohort study	16
11	2015	Rahman N, Murphy CC	Ireland	Retrospective case note review	63
12	2015	Asencio *et al.*	Spain	Retrospective case control study	23
13	2014	Beselga *et al.*	Portugal	Retrospective comparative unicentric institutional study	72
14	2013	Matsuura *et al.*	Japan	Retrospective survey cohort study	53
15	2013	Shorstein *et al.*	US	Retrospective ecological time-trend study	30
16	2012	Haripriya *et al.*	India	Retrospective cohort study	17
17	2010	Wykoff *et al.*	US	Retrospective, consecutive case series	31

Study ID	Year	Authors	Country/ region	Study type	Reference
18	2010	García-Sáenz *et al.*	Spain	Prospective comparative study	24
19	2009	Lloyd JC, Braga-Mele R	Canada	Retrospective, consecutive case series	68
20	2008	Yu-Wai-Man *et al.*	UK	Retrospective analysis	37
21	2007	Endophthalmitis Study Group, European Society of Cataract & Refractive Surgeons	Europe	Prospective randomized partially masked multicenter trial	5
22	2007	Lundström *et al.*	Sweden	Prospective, multicenter, comparative, nonrandomized, observational study	43
23	2007	Moshirfar *et al.*	US	Retrospective, multicenter, observational case series	32
24	2006	Wu *et al.*	Taiwan	Retrospective, comparatice, case-controlled study	74
25	2003	Nagaki *et al.*	Japan	Multicenter study	54
26	2002	Kalpadakis *et al.*	Greece	Retrospective clinical study	61
27	2002	Montan *et al.*	Sweden	Noncontrolled retrospective observational study	44

Study ID	Year	Authors	Country/ region	Study type	Reference
28	2021	Kato *et al.*	Brazil	Retrospective, descriptive, observational study	48
29	2020	Rathi *et al.*	India	Prospective, nonrandomized, comparative, interventional study	18
30	2020	Ma *et al.*	China	Retrospective, comparative, interventional cohort study	59
31	2019	Luz *et al.*	Brazil	Descriptive study of medical records	49
32	2017	Oshika *et al.*	Japan	Prospective case series	55
33	2016	Au *et al.*	Australia	Retrospective longitudinal cohort study	67
34	2016	Creuzot-Garcher *et al.*	France	Cohort study	56
35	2016	Kwok *et al.*	Hong Kong	Retrospective cohort study	70
36	2014	Asencio *et al.*	Spain	Quasi-experimental retrospective study	25
37	2012	Barreau *et al.*	France	Clinical trials	57
38	2012	Romero-Aroca *et al.*	Spain	Prospective, observational study	26
39	2011	Lin *et al.*	China	Retrospective study	60

Study ID	Year	Authors	Country/ region	Study type	Reference
40	2011	Ness *et al.*	Germany	Retrospective clinical study	69
41	2010	Anijeet *et al.*	UK	Retrospective analysis	38
42	2009	Krikonis *et al.*	Greece	Retrospective, observational case series	62
43	2009	Carrim *et al.*	UK	Retrospective consecutive audit	39
44	2009	Al-Mezaine *et al.*	Saudi Arabia	Retrospective observational case series	73
45	2009	Garat *et al.*	Spain	Comparative study	27
46	2008	Kodjikian *et al.*	France	Retrospective cohort study	58
47	2007	Kelly *et al.*	UK	Hospital based retrospective case series	40
48	2007	Mollan *et al.*	UK	Retrospective noncomparative consecutive series	41
49	2006	Patwardhan *et al.*	UK	Single-center study	42
50	2006	Romero *et al.*	Spain	Non-controlled retrospective observational study	28
51	2005	Khan *et al.*	Ireland	Retrospective series	64
52	2005	Wejde *et al.*	Sweden	Prospective survey	45

Study ID	Year	Authors	Country/ region	Study type	Reference
53	2005	Lalitha *et al.*	India	Retrospective, interventional, observational case series	19
54	2005	Jensen *et al.*	US	Retrospective, cross-sectional (prevalence) study	33
55	2004	Buzard K, Liapis S	US	Prospective institutional study	34
56	2004	Wong TY, Chee SP	Singapore	Prospective case series	66
57	2002	Montan *et al.*	Sweden	Prospective survey	46
58	2017	Vieira *et al.*	Brazil	Retrospective clinical registry-based study	50
59	2005	Miller *et al.*	US	Retrospective, observational case series	35
60	2013	Friling *et al.*	Sweden	Prospective epidemiologic study	47
61	2009	Ravindran *et al.*	India	Retrospective observational series	20
62	2015	Schelonka LP, SaBell MA	US	Prospective interventional case series	36
63	2012	Tan *et al.*	Singapore	Cohort study	65

Trends in incidence of POE following cataract surgery

The overall incidence of POE over time was extracted from each of the 63 studies and visually represented as a scatter plot (Fig. 1). The included studies had data points spread over 1993–2017.

For studies with single datapoints, there was evidence of a downward linear trend in the incidence of POE over time (Fig. 2). The risk ratio per year was 0.928, 95% CI [0.911, 0.945], $p < 0.001$. This trend was unchanged when studies using prophylactic IC antibiotics were removed, resulting in a risk ratio of 0.941, 95% CI [0.923,0.959], $p < 0.001$.

A downward linear trend was also observed within studies that had multiple data points and did not utilize any prophylactic IC antibiotics (Fig. 3). The risk ratio per year for these studies was 0.936, 95% CI [0.887, 0.988], $p = 0.017$.

In studies that involved prophylactic IC antibiotics and had multiple data points, the relative risk of POE when no IC antibiotics were used *versus* when IC antibiotics were used was 3.705, 95% CI [3.019,4.547], $p < 0.001$ (Fig. 3). Within these studies, the range of POE incidence in the baseline group was 0.02–1.24%, with a median of 0.29%. The range of POE incidence in patients who received IC antibiotics was 0.00–0.11%, with a median of 0.04%.

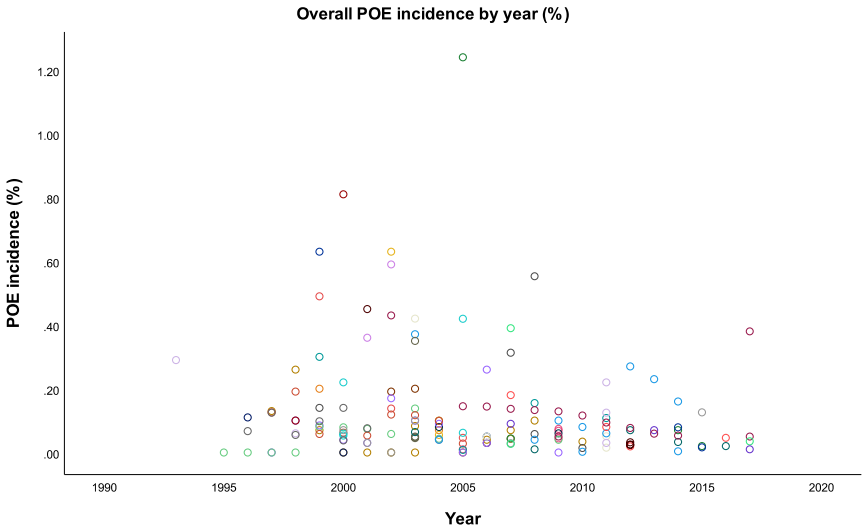

Fig 1. Visual representation of the overall incidence of postoperative endophthalmitis (%) across 1993–2017. Data was collected and compiled from a total of 63 included studies. If studies spanning multiple years did not report annual incidences, the overall incidence was plotted against the median year of the study period.

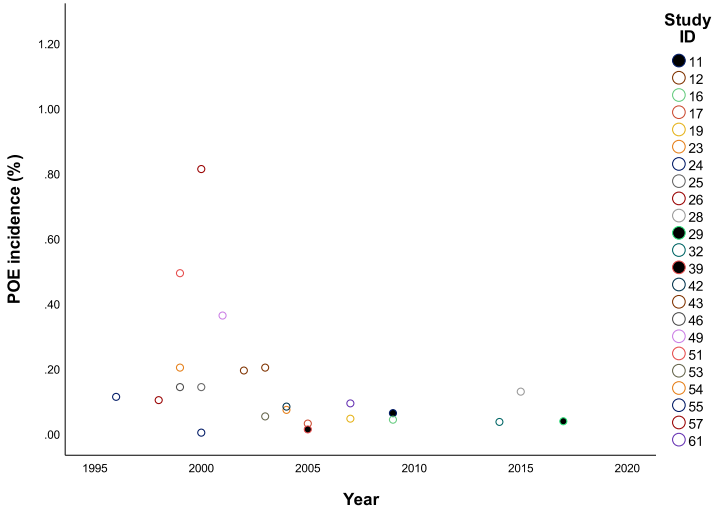

Fig 2. Scatter plot showing postoperative endophthalmitis incidence (%) against year in studies with single datapoints (n = 23). Legend (right) shows the study ID associated with each data point. Studies 11, 29, and 39 (black fill) involved the use of prophylactic intracameral antibiotics.

The overall range of POE incidence in all patients who did not receive IC antibiotics in this review was 0.00–1.24%, with a median of 0.08%. This included patients who were part of studies that did not use any prophylactic IC antibiotics, and the baseline groups in studies that used prophylactic IC antibiotics.

The pooled sample size for each region (Fig. 4) was as follows: India (2,965,980), Europe (1,425,528), United States (215,479), China (155,949), Singapore (94,980), and Australia (14,805). Australia had the highest pooled POE incidence with 0.43% when prophylactic IC antibiotics were not used, followed by Europe (0.20%), Singapore (0.07%), India (0.07%), United States (0.05%), and China (0.03%). When prophylactic IC antibiotics were administered, Australia had the highest POE incidence with 0.05%, then United States (0.04%), Europe (0.04%), India (0.02%), Singapore (0.01%) and China (0.01%).

Discussion

This review shows a downwards trend in POE incidence across 1993–2017 (Figs. 2 and 3). This agrees with current literature describing a perceived drop in POE since the publication of Taban *et al.*'s findings.[75]

Several factors have been proposed to contribute towards this decrease, with one of the most discussed factors being the use of prophylactic IC antibiotics, which has recently become more common in cataract surgeries. In 1998, 75%

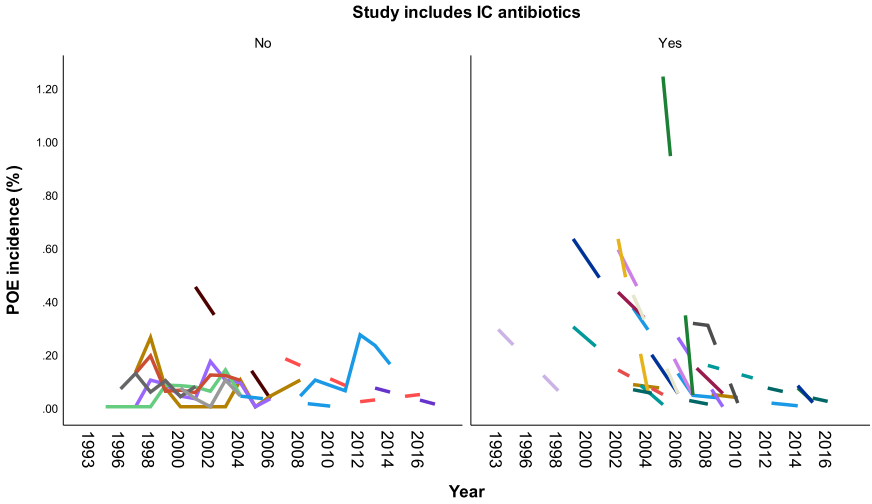

Fig. 3. Line plots showing postoperative endophthalmitis incidence (%) against year in studies with multiple data points, separated into studies including intracameral antibiotic prophylaxis (right; n = 27) and studies not including intracameral antibiotic prophylaxis (left; n = 12).

of Australian ophthalmologists surveyed reported a preference for subconjunctival antibiotics;[76] in 2017, approximately 78.3% of Australian and New Zealand ophthalmologists reported using IC antibiotics.[12] A French study showing a drop in POE incidence from 0.145% to 0.035% attributed the significant reduction to the increased availability of IC cefuroxime injections,[56] and Swedish and Singaporean papers included in this review have identified the non-use of IC antibiotics as a risk factor for POE.[47,65] This review found a significantly reduced risk of POE when IC antibiotics were used: the risk of POE was reduced almost four-fold. Again, our findings are in line with the available literature.[6–8] The median POE incidence in patients that were administered IC antibiotics in our review was 0.04%, which is comparable to the reported average POE rates of 0.03%, 0.02% and 0.01% for IC cefuroxime, moxifloxacin, and vancomycin respectively.[77]

However, it is interesting to note that many of the studies including prophylactic IC antibiotics appear to have high POE rates in their baseline groups (Fig. 3), with the highest reported incidence being 1.24%, which later dropped to 0.04% upon use of prophylactic IC antibiotics.[57] The median POE incidence was 0.29%. In comparison, the median POE incidence in all non-IC antibiotic patients in this review was 0.08%. This is of particular significance, as a common critique of the ESCRS study is that it has a high rate of POE in its control group (0.35%) compared to other studies, and that the perceived benefit of IC antibiotics may therefore be exaggerated.[9] Other concerns surrounding the ESCRS

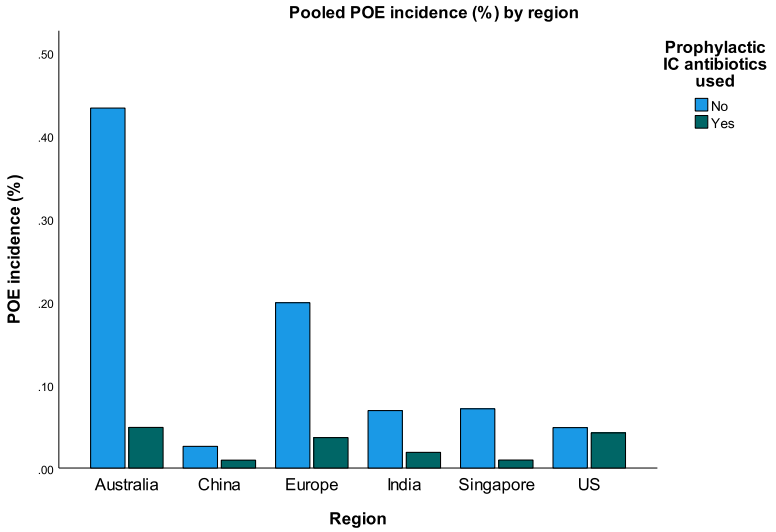

Fig 4. Bar chart of pooled postoperative endophthalmitis (POE) incidence rates (%) by region for the following regions: Australia (n = 1), China (n = 2), Europe (n = 28), India (n = 8), Singapore (n = 2) and US (n = 8). POE incidence was further separated into groups where prophylactic antibiotics were used (green: right) and where they were not used (blue: left).

study include its use of topical levofloxacin instead of fourth-generation fluoroquinolones, the variable surgical techniques causing potential confounding factors, as well as the fact that the study was not blinded for the cefuroxime administration.[3,69,75]

Furthermore, a 2018 Japanese study showed a lower POE incidence of 11/46,741 in eyes not receiving IC antibiotics (0.024%) compared to 2/6,242 eyes receiving IC antibiotics (0.032%). Given the extremely low POE incidence in Japan, the authors felt that routine prophylactic IC antibiotics might be unnecessary.[52] A 2015 study from India that investigated the use of prophylactic IC antibiotics also did not find a significant reduction in POE risk.[16]

The downward linear trend we have reported in our review is significant even when excluding studies that use prophylactic IC antibiotics. This is true for both studies that have single data points (Fig. 2) and studies that have multiple data points (Fig. 3), with both groups having a risk ratio per year of 0.936–0.941. We believe that POE incidence is therefore decreasing worldwide even without the use of prophylactic IC antibiotics, and this could be attributed to multiple factors, *e.g.*, improvement in aseptic techniques, surgical techniques, and surgical equipment.

The pooled POE incidence rates by region allow for some commentary on the differences between each included region (Fig. 4). Australia appears to have the highest POE incidence with and without prophylactic IC antibiotics, as well as the largest reduction in POE rates with IC antibiotics; however, this data is from a single tertiary center in Sydney[67] and has the smallest sample size among all the regions. A 2011 large-scale study of 129,982 patients in Western Australia reported a POE rate of 0.18% between 1980 and 2001,[78] which is lower than the reported rate of 0.43% in the 2016 Australian study included in this review. The 2011 Western Australia study was excluded from this review as it did not describe the use or non-use of prophylactic IC antibiotics.

Europe has the second highest POE incidence without IC antibiotics, and the second largest reduction in POE rates with IC antibiotic administration. The POE incidence of 0.20% is lower than the incidence reported in the 2007 ESCRS control group (0.35%). Interestingly, there is a big difference between Europe's non-IC antibiotic POE incidence and Singapore's non-IC antibiotic POE incidence (0.08%), which is the next highest value. This could be due to the large number of studies ($n = 28$) and heterogeneity of data included in its calculation. The POE incidence with IC antibiotics is comparable with reported values in recent systematic reviews.[77]

The POE incidence for the United States is extremely similar with and without IC antibiotics. This could be related to the relative paucity of IC antibiotic use compared to other regions such as Europe, and therefore a consequent paucity of literature. Studies reporting POE incidence with IC antibiotic use ($n = 2$) were from California and may not be representative of the whole country. These numbers could further explain the ongoing preference for US ophthalmologists to use topical, fourth-generation fluoroquinolones as POE prophylaxis over IC antibiotics. There is currently no FDA-approved antibiotic preparation for IC use in the United States[79] and reconstitution of these antibiotics into preparations for IC use carries a risk of dilutional or dosage errors, which can further increase the risk of toxic anterior shock syndrome.[72] Since studies in the United States that did not use prophylactic IC antibiotics at all ($n = 6$) consistently reported POE rates below 0.05%, the benefit of IC antibiotics is reduced and should be thoroughly weighed against its risks before use. This is similar to Japan, where non-IC antibiotic POE incidence can be lower than POE incidence with IC antibiotics, and where the vast majority of ophthalmologists do not routinely use prophylactic IC antibiotics.

Singapore and India had similar POE rates with and without IC antibiotic prophylaxis, with Singapore having a slightly greater reduction. China had the lowest POE rates both with and without IC antibiotic prophylaxis, although there were only two studies included with a sample size of 155,949, which may not be representative of the whole country.

Limitations

There are several limitations to this review. Firstly, the number of included studies varies between countries and limits our analysis, as some countries are more poorly represented than others. Certain studies that contained large-scale data, *e.g.*, the 2011 Western Australia study and US Medicare studies were excluded as they did not specify the use or non-use of IC antibiotics, which was of interest to us.

Secondly, the heterogeneity of data reporting meant that we had to represent some of the available data differently. While some studies provided an annual breakdown of POE cases and number of cataract surgeries, others only reported the overall number of cases and surgeries across a study period. In order to include them in our analysis, we needed to select a single time point to generate a data point. The nature of this paper is also a limitation: as a review, we are unable to account for the various confounding factors between each paper. It is important to keep this heterogeneity and data collection in mind while interpreting our results.

The continued publication of POE data and prophylactic information in each country is important to understand the natural historical aspect of POE and can also aid in decision-making regarding the use of prophylactic IC antibiotics. A future review that includes more papers and investigates further risk factors for POE would be beneficial in further understanding the time trend of POE incidence.

Conclusion

Our review found that the use of IC antibiotic prophylaxis can reduce POE, and that POE incidence is decreasing worldwide even without the use of prophylactic IC antibiotics. In several studies that purported the benefits of IC antibiotics, the baseline POE incidence in the control groups tended to be higher than the overall worldwide POE incidence.

Our review has also compared the pooled POE incidence between a few different regions. Australia and Europe have the highest rates of POE without IC antibiotics, and the greatest reduction in POE incidence when IC antibiotics are used prophylactically. Singapore, India, and China each had a POE incidence < 0.10% even without prophylactic IC antibiotics, and even lower POE rates after using prophylactic IC antibiotics. United States was the only country to have a POE incidence of 0.04% with a < 0.02% reduction after IC antibiotics use.

While there is evidence for the benefit of IC antibiotics as prophylaxis against POE, we believe that this benefit is most valuable when POE incidence is high. In settings where POE incidence is naturally low, the risks of IC antibiotics could outweigh its benefit. It is therefore important to assess the baseline POE incidence

for each surgical facility thoroughly before implementing the use of IC antibiotics as routine prophylaxis.

Declarations

Ethics approval and consent to participate
Not required.

Consent for publication
Not required.

Competing interests
None to declare.

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

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Abstract

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

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

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

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

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

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

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Introduction

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

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

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

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

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

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

Methods

Search strategy

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

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

Inclusion and exclusion criteria

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

Data extraction

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

Statistical analysis

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

Results

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

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

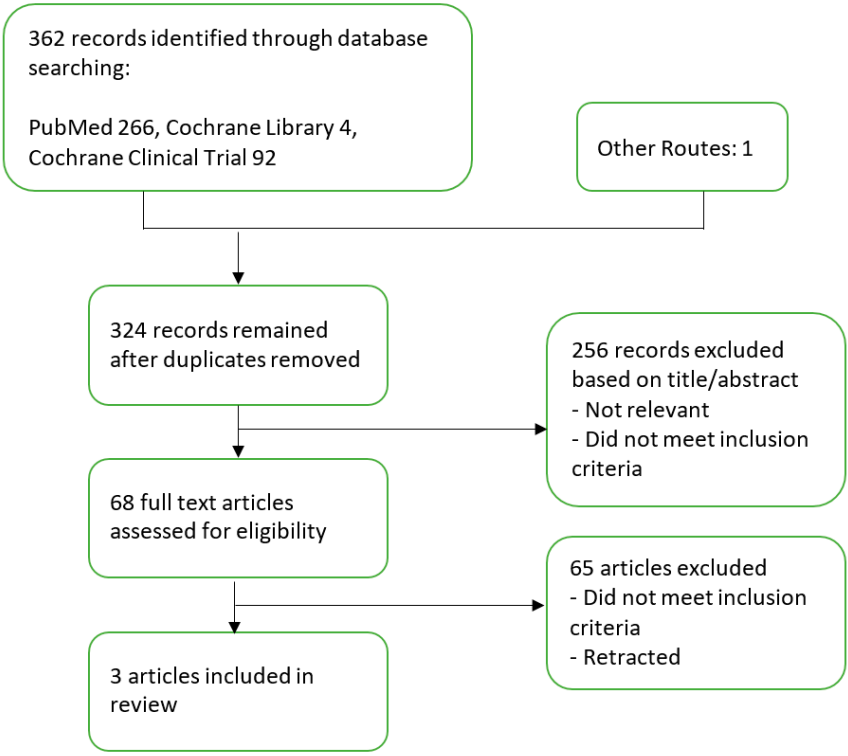

Fig. 1. Flow diagram showing the selection process used to include studies in the review.

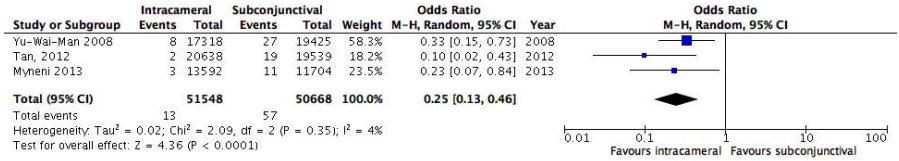

Fig. 2. Forest plot of the rate of postoperative endophthalmitis comparing prophylactic intracameral and subconjunctival antibiotics. The vertical line indicates no difference between the groups. Risk ratios are represented by diamond shapes, and 95% confidence intervals are depicted by horizontal lines.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

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

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

POE: postoperative endophthalmitis

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Conclusion

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

Declarations

Ethics approval and consent to participate

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Consent for publication

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Appendix A. Search strategy

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

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Changes in practice guidelines and regulations in ophthalmology due to COVID-19

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Abstract

Purpose: *Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has been declared as a pandemic by the World Health Organization (WHO). The purpose of the study was to summarize the current recommendations and practice guidelines to be implemented in ophthalmology due to COVID-19.*

Study design: *A systematic review of literature.*

Methods: *A systematic literature search was performed using MEDLINE, EMBASE, CINAHL, Clinical Trials.gov, and ProQuest Dissertations and Theses until May 25, 2020. All conferences held through Association for Research in Vision and Ophthalmology, American Academy of Ophthalmology, and Canadian Society of Ophthalmology were also searched until May 25, 2020. Eligible articles were identified by reviewing the retrieved results.*

Results: *In total, 57 records were retrieved from multiple databases and 0 records were identified through grey literature search. Ten articles were included for analysis. Rigorous hand hygiene, proper screening, and proper use of protective personal equipment by both staff and patients were strongly advised. Careful triage of patients upon arrival to facilities based on screening was advised along with deferral of any non-urgent appointments and implementing measures to limit exposure in waiting rooms. Routine disinfection of equipment, use of shields or barriers on slit lamps, and limiting the use of instruments and tests were strongly recommended and advised.*

Conclusions: *The implementation of guidelines should be in place for ophthalmologic staff, facilities, and visitors to help minimize the spread of COVID-19 and promote a safer environment in ophthalmology.*

Keywords: *COVID-19, coronavirus, guidelines, ophthalmology, practice*

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] On March 11, 2020, the World Health Organization (WHO) declared COVID-19 outbreak a pandemic. COVID-19 can cause severe acute respiratory infection with an incubation period of 1–14 days.[2] Common symptoms of COVID-19 can consist of fever, dry cough, and fatigue.[3] It can be mainly spread through respiratory droplets; however, spread through various discharges, feces, aerosol, and conjunctiva have also been suspected.[4] Early on, in February 2020, it was reported by the National Health Commission of the People's Republic of China that 3,387 healthcare workers had confirmed infected COVID-19.[3] More recently, since April 2020, over 2,000,000 people from 210 countries have been infected.[1] The death toll has been shown to be greater than 140,000 people worldwide, with a case fatality rate of 6.7%.[1]

With health care workers operating on the frontlines, they are constantly at high risk of infection to the SARS-CoV-2. Like many health care workers, ophthalmologists are very much at risk of COVID-19 infection. In fact, the ophthalmologist Li Wenliang was one of the first people to recognize the outbreak of COVID-19 and become infected.[5] Since many ophthalmic examinations such as slit-lamp examinations are commonly performed in a setting with close contact with patients, the risk of exposure of ophthalmologic staff to infection can be quite high.

Various recommendations and guidelines have been put in place to help protect both health care workers as well as patients from the spread of COVID-19. Currently, there is a need to address how to best provide ophthalmic care for patients during this pandemic. Establishing guidelines is necessary to ensure that there is a strategy of protection during clinical practice. The purpose of this study is to summarize the current practice guidelines and recommendations to be implemented in ophthalmology due to COVID-19 by systematically reviewing the literature.

Methods

Search methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements[6] were used to conduct this systematic review. Database searches were executed on MEDLINE, EMBASE, CINAHL. Clinical Trials.gov, and ProQuest dissertations and theses to locate studies investigating ophthalmology, practice, guidelines, and COVID-19. Search strategies were designed for each database (Appendix A) to find the most relevant studies until May 25, 2020. OVID® AutoAlerts for MEDLINE and EMBASE were set up to send monthly

updates regarding any relevant new literature. No limits were placed throughout the searches.

A grey literature search was performed through conferences held by the Association for Research in Vision and Ophthalmology (ARVO) and the American Academy of Ophthalmology (AAO) in all years available. Conferences held through the Canadian Society of Ophthalmology (COS) were searched from the year 2010 to 2020. Keywords that were used to search through conference abstracts were "covid-19 or coronavirus or coronavirus infection* or 2019-nCoV or SARS-CoV-2 or nCoV or covid*", "regulation* or guideline* or practice*", and "ophtha*". The searches for ARVO, AAO, and COS were all done until May 25, 2020.

Study inclusion and exclusion criteria

Studies pertaining to changes in guidelines, practice, or regulations in ophthalmology were included with this being the primary focus of the current study. Clinical trials, comparative studies, and case series were included. Narrative reviews, perspectives, and articles where large groups convened to establish guidelines were also included. Editorials and letters on any relevant recommendations or guidelines in ophthalmology were included. Non-human studies were excluded from analysis. Only studies with full text articles in English were included and no restrictions were placed on the country in which the study was performed.

Screening

The results of each database search were imported into Covidence (Covidence Systematic Review Software, Veritas Health Innovation, Melbourne, Australia). Upon import, duplicates were removed, and the systematic screening was performed by two independent reviewers (B.Y and B.H). Title and abstract screening were then carried out, and Cohen's kappa coefficient was calculated after each level of screening before resolving conflicts. Conflicts were resolved by consensus and if consensus was not reached, then a third reviewer was required to resolve any disagreements. For full-text screening, the full texts of any studies that had made it past abstract screening were uploaded. Cohen's kappa was once again calculated before conflicts were resolved. A finalized list of literature was then scored for quality.

Risk of bias assessment and data extraction

Risk of bias (RoB) was assessed to ensure completeness of our methodology. The RoB assessment was performed using the AMSTAR quality assessment tool[7] for the review articles. Various items were examined using the AMSTAR tool, including question and inclusion, protocol, study design, comprehensive search, study selection, data extraction, excluded studies justification, included studies details, RoB, funding sources, statistical methods, RoB on meta-analysis, RoB in individual studies, explanation for heterogeneity, publication bias, and conflict

of interest. All studies were then given an overall quality rating. Due to limited evidence, none of the lesser quality articles were excluded from the analysis.

One investigator (B.Y) performed the data extraction. Information on the characteristics of each study was extracted from the ten articles. This information included the first author's last name, year of publication, country of origin, study design, and sources of funding. Other data extracted included the specific guidelines, changes in practice, and regulation changes applicable to ophthalmologic staff, patients, and facilities.

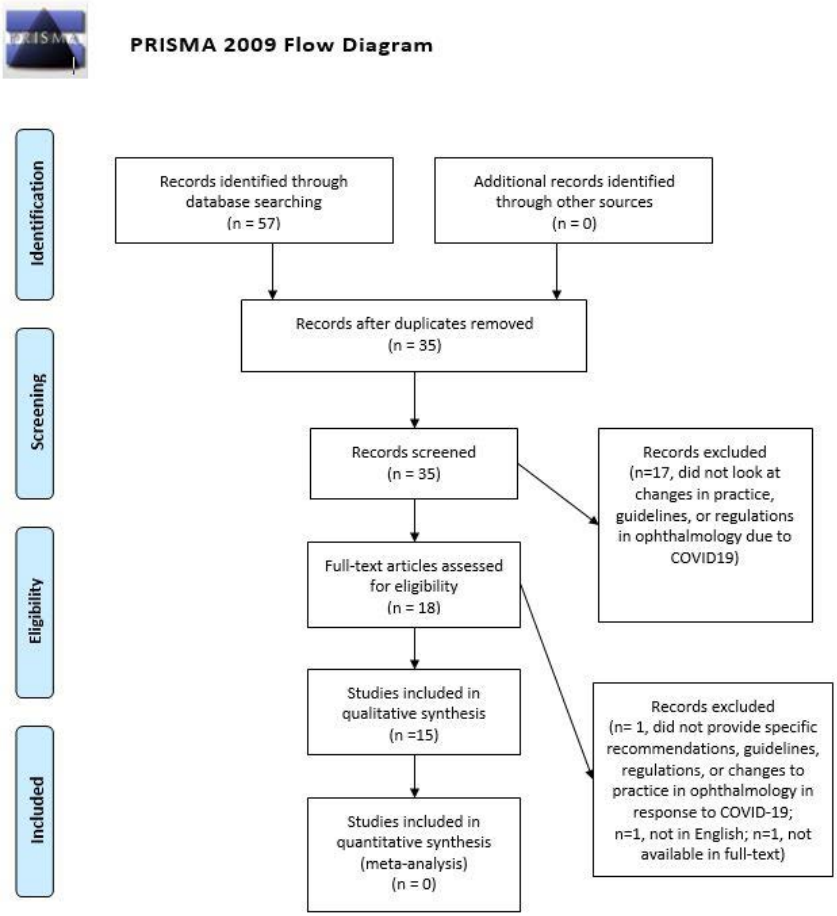

Fig. 1. PRISMA flowchart summarizing the results of the literature search.

Results

Search results and study characteristics

Upon completing database searches, 57 potentially relevant studies were produced (Fig. 1). All studies were imported into Covidence, where 22 duplicates were removed before screening. The remaining 35 studies underwent level 1 screening for their titles and abstracts. Seventeen studies were excluded because they did not look at changes in practice, guidelines, or regulations in ophthalmology due to COVID-19. The remaining 18 studies underwent level 2 screening for their full texts. One study was excluded because it did not provide specific recommendations or changes to practice in ophthalmology in response to COVID-19, another study was excluded because the full-text article was not available in English, and another one study was excluded because the full-text article was unavailable.[8] The final 15 studies were included in data extraction. Five of the studies were reviews and their RoB was assessed using AMSTAR risk of bias assessment instruments[7] (Appendix C). For the rest of the ten studies, five studies were letters and opinion pieces and the other five were perspective studies.

Cohen's kappa values for the agreement between the two reviewers were 0.52 and 1.00 for levels 1 and 2 screening, respectively (Appendix B).

The characteristics of ten included studies (out of a total of 15, since five were letters, comments, and opinions) are summarized in Table 1. These studies were conducted in various countries, including the United Kingdom, United States, China, France, Singapore, Italy, Iran, and India. Five studies were review articles, two studies were editorials, two studies were letters to the editor, one study was a commentary, and five studies were perspective articles. Data pertaining to specific guidelines or changes in practice applicable to ophthalmologic staff, patients, and facilities can be found summarized in Table 2, Table 3, and Table 4 respectively.

Guidelines for practice for staff and patients in ophthalmology

Eleven articles[1,9,10–18] emphasized rigorous hand hygiene practice for staff as a key preventive measure. Ten articles[9,11,13–16,18–21] recommended regular symptom and temperature screening of staff. All 15 articles[1,9–22] encouraged the use of personal protective equipment (PPE) by working staff with the use of face masks being particularly emphasized to prevent droplet transmission. It is recommended by one article[9] for staff to wear a N95 or FFP2 mask wherever possible. However, nine articles[1,11–14,16,18–22] recommended for staff to wear such masks and full PPE (including a cap, gloves, gowns, eye protection, and face shields) when attending persons under investigation and confirmed with COVID-19. It is also recommended by three[13,20,22] of the previous nine articles to simply wear surgical masks during low-risk encounters rather than N95 or FFP2 masks.

Table 1. Characteristics of included studies

Author	Year	Study design	Study location	Funding information	Primary focus
Bacherini *et al.*[15]	2020	Perspective	Italy	-	To review how SARS-CoV-2 affects the eye and discuss implications for ophthalmologists.
Korobelnik *et al.*[9]	2020	Review	France	Writing and editorial assistance was provided by Hollie Robinson, PhD of Complete Health-Vizion, Ltd., McCann Health Medical Communications, funded by Bayer Consumer Care AG, Pharmaceuticals, Basel, Switzerland.	To discuss key considerations for managing patients with retinal disease during the COVID-19 pandemic.
Lai *et al.*[16]	2020	Perspective	China	-	To share the experience of a single center's infection control measures in ophthalmology.
Lam *et al.*[1]	2020	Perspective	China	-	To share protocols and experiences in the prevention of infection in the current COVID-19 outbreak. To answer the key frequently asked questions in relevant areas.
Lim *et al.*[11]	2020	Perspective	Singapore	-	To describe the impact of COVID-19 in a single practice and share strategies and guidelines to maintain a sustainable ophthalmology practice.
Mishra *et al.*[10]	2020	Perspective	United States	None.	To list practice considerations to limit COVID-19 transmission in the proton ocular treatment setting for uveal melanoma.
Romano *et al.*[12]	2020	Review	Italy	None.	To provide useful guidelines, targeted at ophthalmology professionals, to minimize COVID-19 infection of both health-care workers and patients based on literature and experience.
Safadi *et al.*[17]	2020	Review	Israel	None.	To present an established practice protocol for ophthalmic practice during the COVID-19 pandemic.
Sengupta *et al.*[14]	2020	Review	India	None.	To develop a preferred practice pattern based on consensus discussion between some of the leading ophthalmologists in India, major institutional representatives, and the AIOS leadership.
Yu *et al.*[21]	2020	Review	China	Supported by the Natural and Science Foundation of China (Grant No. 81570869), and Wenzhou Key Team of Scientific and Technological Innovation (Grant No. C20170002).	To summarize the Chinese experience against SARS-CoV-2 in ophthalmology in a literature review.

-: information not present; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Table 2. Guidelines and recommendations for ophthalmologic staff

Author	Year	Rigorous hand hygiene	Symptom and/or temperature screening	PPE
Bacherini *et al.*	2020	Yes.	Yes.	Yes. Surgical masks and goggles for ophthalmologists. Surgical/N95 respirator masks, as well as gloves and water-resistant gowns and visors.
Korobelnik *et al.*	2020	Yes.	Yes.	Yes. N95 or FFP2 mask is preferable wherever possible. If either are unavailable, then a surgical mask should be worn. Full PPE worn when dealing with COVID-19 cases.
Lai *et al.*	2020	Yes.	Yes.	Yes. Face masks for all personnel. Isolation gowns, N95 respirators and protective eyewear when attending COVID-19 cases.
Lam *et al.*	2020	Yes.	-	Yes. Face masks should be worn by all personnel. Full PPE worn when dealing with COVID-19 cases.
Li *et al.*	2020	-	Yes.	Yes. Proper use of PPE with proper training. N95 mask and eye protection for staff dealing with persons under investigation and confirmed with COVID-19.
Lim *et al.*	2020	Yes.	-	Yes. For high-risk patients, full PPE is always worn by all involved health care workers. Use of visor masks or coverspecs over the use of goggles during surgery. Use of goggles and N95 masks for all staff within the operating theater during emergency surgery.
Ma *et al.*	2020	-	-	Yes. Low-risk encounter PPE: gown, surgical mask, disposable cap. Moderate-risk encounter PPE: water-repellent gown, barrier apparel, surgical mask or N95 respirator, disposable cap, gloves, goggle or face shield, shoe covers. High-risk encounter PPE: water-repellent gown, barrier apparel, N95 respirator, disposable cap, double gloves, goggle or face shield, shoe covers.
Mishra *et al.*	2020	Yes.	Yes.	Yes. Appropriate masking. Gloves, mask, face shield, goggles, hair cover when in close contact with patients.
Moravvej *et al.*	2020	-	Yes.	Yes. Latex gloves, eye protection, a surgical-style face mask, a long-sleeved fluid-resistant gown, and disposable shoe covers for attending staff.
Romano *et al.*	2020	Yes.	Yes.	Yes. Ophthalmologists attending patients with suspected or confirmed cases of COVID-19 need to wear at least FFP2. Long-sleeved waterproof gowns and gloves should be used if exposed to COVID-19 positive patients. Goggles and eye protection for ophthalmologists.
Safadi *et al.*	2020	Yes.	Yes.	Yes. Masks and eye protection when caring for patients potentially infected with COVID-19.
Seah *et al.*	2020	Yes.	-	Yes. Full PPE for emergency operations.
Sengupta *et al.*	2020	Yes.	Yes.	Yes. Protections for head, mouth, nose, and eye (with a surgical cap, three-ply surgical mask, goggles/face shield) for the examiner and a three-ply surgical mask for the patient.
Williams *et al.*	2020	Yes.	-	Yes. General cases: disposable cap, eye protection, surgical mask, gown. Suspect cases: use of a face shield, an N95 mask, and disposable gloves.
Yu *et al.*	2020	-	Yes.	Yes. Caps, respiratory protection, gloves, gowns, eye protection, and face shields are used for personal protection.

-: information was not present; PPE: personal protective equipment

Table 3. Guidelines and recommendations for ophthalmologic patients

Author	Year	Rigorous hand hygiene	Symptom and/or temperature screening	Use of PPE
Bacherini *et al.*	2020	-	Yes.	Yes. Surgical masks and gloves should be worn by patients.
Korobelnik *et al.*	2020	Yes.	Yes.	Yes. Surgical mask should be worn patient.
Lai *et al.*	2020	-	Yes.	Yes. Surgical masks.
Lam *et al.*	2020	Yes.	Yes.	Yes. Face masks should be worn by all personnel and visitors.
Li *et al.*	2020	-	Yes.	Yes. Masking of urgent patients with respiratory symptoms, suspect or confirmed with COVID-19.
Lim *et al.*	2020	Yes.	-	-
Ma *et al.*	2020	-	Yes.	Yes. Patients should wear masks.
Mishra *et al.*	2020	Yes.	Yes.	Yes. Appropriate masking.
Moravvej *et al.*	2020	-	Yes.	-
Romano *et al.*	2020	Yes.	Yes.	Yes. Surgical mask for patients.
Safadi *et al.*	2020	Yes.	Yes.	-
Seah *et al.*	2020	Yes.	-	-
Sengupta *et al.*	2020	Yes.	Yes.	Yes. Three-ply face masks for all patients.
Williams *et al.*	2020	Yes.	Yes.	Yes. Masks.
Yu *et al.*	2020	-	Yes.	Yes. Every patient should wear a mask.

PPE: personal protective equipment; -: information was not present

Table 4. Guidelines and recommendations for ophthalmologic facilities

Author	Year	Triage of patients based on screening	Surface and equipment disinfection	Slit-lamp shield	Deferral of non-urgent appointments	Limiting use of equipment and testing	Minimizing the number patients and distancing in waiting rooms	Telemedicine consultation
Bacherini *et al.*	2020	Yes.	Yes.	Yes.	Yes.	-	Yes.	-
Korobelnik *et al.*	2020	-	Yes.	Yes.	Yes.	Yes.	Yes. Enforcing a 1- or 2-meter distance between people.	Yes.
Lai *et al.*	2020	Yes.	Yes.	Yes.	Yes.	-	Yes.	-
Lam *et al.*	2020	Yes.	Yes.	Yes.	-	-	Yes. Keeping at least 1-meter distance from others.	-
Li *et al.*	2020	-	Yes.	Yes.	-	-	-	Yes.
Lim *et al.*	2020	Yes.	Yes.	-	-	-	-	-
Ma *et al.*	2020	Yes.	Yes.	Yes.	Yes.	-	-	-
Mishra *et al.*	2020	-	Yes.	-	Yes.	-	Yes.	Yes.
Moravvej *et al.*	2020	-	Yes.	Yes.	Yes.	-	Yes. Safe distance (1.5 meters) was assured between patients.	-
Romano *et al.*	2020	-	Yes.	Yes.	-	-	Yes. At least 2 meters from one another.	-
Safadi *et al.*	2020	Yes.	Yes.	Yes.	Yes.	-	Yes.	Yes.
Seah *et al.*	2020	-	Yes.	-	Yes.	-	-	-
Sengupta *et al.*	2020	Yes.	Yes.	Yes.	Yes.	Yes.	Yes. Maintain 1-meter distance.	Yes.
Williams *et al.*	2020	Yes.	Yes.	Yes.	Yes.	Yes.	Yes. Six feet apart.	Yes.
Yu *et al.*	2020	-	Yes.	Yes.	Yes.	Yes.	Yes. At least 1.5 meters apart from one another when in registration and waiting area.	-

PPE: personal protective equipment; -: information was not present

Nine[1,9–13,16–18] of the eleven articles that emphasized hand disinfection for staff also emphasized this practice for patients and visitors. Thirteen articles[1,9,10,12,14–21] recommended that regular symptom and temperature screening be done for patients prior to or upon arrival to their appointments. The use of PPE by patients and visitors is strongly recommended by eleven articles;[1,9,10,12,14–16,18,19,21,22] however, these articles simply advised patients and visitors to wear surgical masks during visits.

Guidelines for facilities in ophthalmology

Proper triage of patients based on temperature and symptom screening upon entry to an ophthalmologic facility is advised in eight articles.[1,10,13–17,22] These same eight articles recommended that patients negative for COVID-19-suspect criteria can pass through with their visit; however, the attending physician should be informed about any suspect patient and assess their need for a same-day consultation. For patients who cannot but should attend a clinic in person, the use of telemedicine consultations was strongly encouraged by six articles.[9,13,16–19] Telemedicine consultations were also encouraged to be used whenever possible to reduce the number of visitors. Routine and proper disinfection of equipment and surfaces that are commonly touched is strongly advised in all included articles.[1,9–22] It is recommended that povidone-iodine, a combination of chlorhexidine with ethanol and cetrimide, alcohol-based solutions (75% ethanol), or other lipid solvents ether (chlorine disinfectant, peracetic acid, chloroform) be used as disinfectants.[10,22] Exposure of equipment to 56°C for 30 min was also advised by one article.[22] Twelve articles[1,9,11,13–17,19–22] advised the use of shields or barriers on slit-lamps due to there being a large risk of exposure during this type of examination. It was also advised in four articles[9,13,17,21] to limit the use of instruments and tests to only those deemed as critical for decision-making.

Eleven articles[9,12,13–18,20–22] strongly recommended or implemented the differing of any non-urgent appointments. It was recommended by Ma *et al.*[22] to only consider taking cases that were ocular emergencies, such as eye traumas, acute glaucoma, rhegmatogenous retinal detachment, and central retinal artery occlusion. In the article by Korobelnik *et al.*,[9] it was noted that patients with neovascular age-related macular degeneration, neovascular glaucoma, new cases with significant vision loss, new central retinal vein occlusion cases, as well as monocular or quasi-monocular patients were considered as emergent and should be prioritized. Finally, it is also advised by six articles[1,9,11,13–18,20,21] to limit exposure in waiting rooms by enforcing a safe distance between visitors and minimizing the number of people within these rooms.

Discussion

The rapid spread of COVID-19 resulted in a multitude of recommendations and guidelines to be followed in the practice of ophthalmology. In this report, we summarized the current general recommendations as well as changes implemented in practice guidelines due to COVID-19 in ophthalmology for staff, patients, and facilities. Various bibliographic database searches as well as the grey literature search were performed.

Fifteen studies were included for qualitative analysis in this review. Characteristics of the included studies such as study design, study location, and primary focus were summarized. The findings from this study demonstrated rigorous hand hygiene,[1,9,10–18] temperature and symptom screening,[1,9,10,12,14–21] and proper use of PPE[1,9–22] by both staff and patients as important preventative measures that are currently recommended. The proper triage of patients upon arrival to ophthalmologic facilities based on screening[1,10,13–17,22] in conjunction with the deferral of non-emergent visits[9,12–18,20–22] are also important measures that should be taken to minimize exposure. Implementing measures such as distancing and limiting the number of people in waiting rooms is a commonly used strategy in many ophthalmologic facilities.[1,9,11,13,20,21] The routine disinfection of equipment using proper cleaning solutions,[1,9–22] the use of shields or barriers on slit-lamps,[1,9,11,13–17,19–22] and limiting the use of instruments and tests[9,13,17,21] were strongly recommended and advised.

Limitations of the present study include the deficits of the literature that were included. COVID-19 is a new disease with minimal research currently available. As a result, some of the articles included were letters to the editor and editorials.[12,19,20,22] Many of the articles[9–11,13] were reviews lacking a thorough search strategy or were perspectives and opinions based off clinical experience only. However, many of these strategies and guidelines were put together by professional clinicians and institutional representatives. Most of the included articles were from countries in Asia or Europe. However, it should be noted that the articles by Korobelnik *et al.*,[9] Li *et al.*,[19] and Mishra *et al.*,[10] were written by authors from a mixture of various countries, potentially providing a somewhat global perspective.

Conclusions

This systematic review has shown that proper precautions and guidelines should be taken by ophthalmologic staff, facilities, and visitors to help minimize the spread of COVID-19 and promote a safer environment in ophthalmology. In the event of a future outbreak of SARS-CoV-2 or another infectious agent, effective changes to practice guidelines should be established quickly.

Declarations

Ethics approval and consent to participate
Not required.

Consent for publication
Not required.

Competing interests
The authors have no conflicts of interests to declare that may be affected by the publication of the paper.

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Appendix A. Search strategies for all databases

Table 1. Medline

#	Searches	Results
1	Coronavirus Infections/ or Coronavirus/ or covid-19.mp.	20044
2	(2019-nCoV or SARS-CoV-2 or nCoV or covid*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	16453
3	1 or 2	21659
4	ophtha*.mp. or Ophthalmology/	153175
5	3 and 4	103
6	regulation*.mp. or Government Regulation/	1452528
7	Social Control, Formal/	11787
8	Health Plan Implementation/ or implementation*.mp.	250514
9	practice.mp. or Practice Guideline/	1017263
10	6 or 7 or 8 or 9	2650124
11	5 and 10	28 (05/25/2020)

Table 2. EMBASE

#	Searches	Results
1	SARS coronavirus/ or Coronavirinae/ or Coronavirus infection/ or covid-19.mp.	19009
2	(2019-nCoV or SARS-CoV-2 or nCoV or covid*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	18642
3	1 or 2	25940
4	ophthalmology/ or ophtha*.mp.	212824
5	3 and 4	166
6	regulation*.mp.	1632394
7	practice.mp. or practice guideline/ or clinical practice/	1599841
8	6 or 7	3195651
9	5 and 8	27 (05/25/2020)

Table 3. CINAHL

Search ID#	Search terms	Results
S1	(MH "Coronavirus Infections") OR (MH "SARS Virus") OR "covid-19 or coronavirus or 2019-ncov" OR (MH "Coronavirus")	1,605
S2	"ophtha*" OR (MH "Ophthalmic Nursing") OR (MH "Ophthalmic Equipment and Supplies")	24,261
S3	(MH "Ophthalmology") OR "ophthalmology"	7,959
S4	(S2 OR S3)	24,261
S5	(MH "Practice Guidelines") OR "practice guidelines" OR (MH "Rules and Regulations")	92,433
S6	"regulation" OR (MH "Government Regulations")	88,532
S7	S5 OR S6	177,977
S8	S1 AND S4	1
S9	S7 AND S8	1 (05/25/2020)

Grey literature

1. **Clinical Trials – https://clinicaltrials.gov/ (Searched May 25, 2020)**
    a. (regulation* or guideline* or practice*) and ophtha* | Covid-19|
    b. 0 results

2. **ProQuest – Dissertations and Theses (Searched May 25, 2020)**
    a. (covid-19 or coronavirus or coronavirus infection* or 2019-nCoV or SARS-CoV-2 or nCoV or covid*) AND (regulation* or guideline* or practice*) AND ophtha*
        i. 319 results
    b. noft(covid-19 or coronavirus or coronavirus infection* or 2019-nCoV or SARS-CoV-2 or nCoV or covid*) AND noft(regulation* or guideline* or practice*) AND noft(ophtha*)
        i. 0 results

3. **Conference Proceeding Searches**

Conference	Link	Years searched	Search terms	Results/Comments
ARVO	https://arvojournals.org/index.aspx	All years	"Meeting abstract" AND (covid-19 or coronavirus or coronavirus infection* or 2019-nCoV or SARS-CoV-2 or nCoV or covid*) AND (regulation* or guideline* or practice*) AND (ophtha*)	Searched through meeting abstracts 0 results (05/25/2020)
AAO All Meetings	https://secure.aao.org/aao/meeting-archive	"All years available"	Topic: All topics Keywords: "covid-19 or coronavirus or coronavirus infection* or 2019-nCoV or SARS-CoV-2 or nCoV or covid*", "regulation* or guideline* or practice*", "ophtha*"	No relevant abstracts/presentations found (05/25/2020)
COS	http://www.cos-sco.ca/cpd/annual-meeting/	010-2020	"covid-19 or coronavirus or coronavirus infection* or 2019-nCoV or SARS-CoV-2 or nCoV or covid*", "regulation* or guideline* or practice*", "ophtha*"	Searched through abstracts and presentations No relevant abstracts/presentations found (05/25/2020)

Appendix B. Cohen's Kappa statistic for screening

Table 4. Kappa statistics (title screening)

Review authors	B.H.				
B.Y.		Include	Exclude	Unsure	Total
	Include	12	2	3	**17**
	Exclude	2	12	2	**16**
	Unsure	1	0	1	**2**
	Total	**15**	**14**	**6**	**35**

$$Kappa = \frac{P(O) - P(E)}{1 - P(E)}$$

$$P(O) = \frac{12 + 12 + 1}{35}$$

$$P(O) = 0.714285714$$

$$P(E) = \frac{(17x15) + (16\,x14) + (2\,x6)}{35^2}$$

$$P(E) = 0.400816327$$

$$Kappa = \frac{P(O) - P(E)}{1 - P(E)}$$

$$Kappa = \frac{0.714285714 - 0.400816327}{1 - 0.400816327}$$

$$\underline{\boldsymbol{Kappa = 0.523160763}}$$

Table 5. Kappa statistics (full-text screening)

Review authors		B.M.		
B.Y.		Include	Exclude	Total
	Include	15	0	**15**
	Exclude	0	3	**3**
	Total	15	3	**18**

$$\underline{\boldsymbol{Kappa} = \mathbf{1}}$$

Appendix C. Scores from study quality assessment

Table 6. Scores from study quality assessment

Study	Year	Question and inclusion	Protocol	Study design	Comprehensive search	Study selection	Data extraction	Excluded studies justification	Included studies details	RoB	Funding sources	Statistical methods	RoB on meta-analysis	RoB in individual studies	Explanation for heterogeneity	Publication bias	Conflict of interest	Overall quality
Korobelnik *et al.*	2020	Yes	Partial yes	No	No	Yes	Yes	No	No	No	No	N/A	N/A	No	No	N/A	Yes	Critically low
Romano *et al.*	2020	Yes	Partial yes	Yes	Yes	Yes	Yes	No	No	No	No	N/A	N/A	No	No	N/A	Yes	Critically low
Safadi *et al.*	2020	Yes.	Partial yes	No	Yes	No	No	No	No	No	No	N/A	N/A	No	No	N/A	Yes	Critically low
Sengupta *et al.*	2020	Yes	Partial yes	Yes	No	Yes	Yes	No	No	No	No	N/A	N/A	No	No	N/A	Yes	Critically low
Yu *et al.*	2020	Yes.	Partial yes	Yes	Yes	Yes	Yes	No	No	No	No	N/A	N/A	No	No	N/A	Yes	Critically low

N/A: not applicable, RoB: risk of bias

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Efficacy of atropine eyedrops in reducing myopia progression and axial elongation in myopic children: a meta-analysis

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Abstract

Purpose: *To determine the efficacy of various concentrations of atropine eyedrops on retarding myopia progression and axial elongation in Asian children.*

Study design: *Meta-analysis.*

Methods: *Randomized clinical trials and prospective interventional non-randomized studies which enrolled children aged 4 to 14 years old who received atropine treatment for myopia were included in the study. The Cochrane Collaboration 6 aspects of bias was used to assess the risk of bias for all included studies. Outcome measures were myopia progression and axial elongation. Meta-analysis was conducted using the random-effects model.*

Results: *Eight randomized clinical trials and two prospective interventional non-randomized studies which included a total of 1,229 Asian children were included in the analysis. The pooled mean difference between control and atropine for myopia progression was 0.77 diopters (D) per year [CI 0.64, 0.89]. Subgroup analysis by concentration showed a decreasing trend with decreasing concentration. The pooled mean difference of myopia progression for 1%, 0.5%, 0.25%, and 0.1–0.125% atropine was 0.97 D/year [CI 0.72, 1.21], 0.88 D/year [CI 0.74, 1.02], 0.79 D/year [CI 0.37, 1.21], and 0.80 D/year [CI 0.62, 0.97], respectively; whereas that for 0.01% atropine was 0.46 D/year [CI -0.02, 0.94] indicating that this intervention may or may not be favorable for slowing myopia progression. The pooled mean difference between control and atropine for axial elongation was -0.22 mm [CI -0.29, -0.14] favoring atropine. Subgroup analysis by concentration also showed decreasing trend with decreasing concentration. The pooled mean difference of axial elongation for 1%, 0.5%, 0.1%, 0.05%, and 0.025% atropine was -0.44 mm [CI -0.57, -0.32], -0.19 mm [CI -0.35, -0.04], -0.10 mm [CI -0.17, -0.03], -0.21 mm [CI -0.28, -0.14], and -0.12 mm [CI -0.16, -0.08], respectively; whereas that for 0.01% atropine was -0.01 mm [CI -0.09, 0.06] indicating that this intervention may or may not be favorable in reducing axial elongation.*

Conclusion: *This meta-analysis shows that the effects of atropine for both myopia progression and axial elongation are dose-dependent for the concentration 0.025% to 1%. Results for 0.01% atropine are still equivocal.*

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Keywords: *atropine, Asian children, axial elongation, meta-analysis, myopia progression*

Introduction

Myopia is the most common ocular condition and has been increasing in prevalence, particularly in East Asia. In certain countries such as Singapore, Hong Kong, and Taiwan, the prevalence of myopia has reached 80% or even higher in the young adult population.[1] Likewise in the United States, the prevalence rose from 25% to 42% between 1971 and 1999.[2] Studies have also shown that myopia has been increasing in younger age groups from 5.8% in 1983 to 61% in 2000 in 7-year-old children in Taiwan.[3] Prevention of myopia progression is critical due to the risks and complications associated with it such as retinal detachment, cataract, glaucoma, choroidal neovascularization, and myopic degenerative changes.[4] Epidemiological studies done in Asian areas found that retinopathy secondary to high myopia has become the second most frequent cause of low vision and blindness among adults.[5]

Several treatment methods have been studied with the aim of retarding myopia progression in children. These treatment methods include eyeglasses that undercorrect, multifocal eyeglasses, novel lens eyeglasses design, various contact lens therapies such as bifocal or multifocal contact lenses or orthokeratology, topical timolol, and topical antimuscarinic agents including pirenzepine and atropine.[2] A Cochrane database review done by Walline *et al.* concluded that antimuscarinic agents are the most likely effective treatment to slow myopia progression.[6] This review compared various antimuscarinic agents to placebo, with a subgroup analysis of atropine that included only two studies that were available at the time.

Atropine is a nonselective muscarinic antagonist which has been used in myopia control for the past few decades. However, there is still no ideal approach as to the concentration and duration of atropine treatment for the control of myopia progression.[1] Several clinical trials have already been conducted to determine the most effective and safest dosing in reducing myopia progression while minimizing adverse effects inherent to atropine, such as photophobia and blurred near vision.[5] The exact mechanism by which atropine reduces myopia progression is still not clearly understood. Previously, it was thought that accommodation has a role in retarding myopia progression, but studies have demonstrated that atropine was able to inhibit myopia in animals that have no capacity for accommodation. Another theory states that atropine may have a role in remodeling of the sclera.[7] However, current theories suggest that pupillary dilation may result in increased ultraviolet A exposure, which limits axial elongation, or that myopia may be associated with increased chronic inflammation in the eye, which may be downregulated by atropine.[2]

A meta-analysis by Song *et al.*[3] in 2011 showed that the effect of atropine increased with higher doses, suggesting a dose-dependent effect. However, a more recent meta-analysis by Gong *et al.*[1] in 2017 found no significant difference between various doses of atropine, with 0.01% dose as its lowest concentration. The first meta-analysis[3] in 2011 reviewed only six studies, with 0.1% dose as its lowest concentration. More recent clinical trials with lower concentrations have since been conducted to determine the lowest effective concentration with the least adverse effects, such as photophobia, blurred near vision, and allergic reactions. The 2017 meta-analysis by Gong *et al.*[1] combined different types of studies (randomized clinical trials and cohort studies) due to lack of availability of studies examining each atropine concentration. Furthermore, axial length was also not evaluated across various doses of atropine because results were only available in higher doses.

The objective of this study is to determine the efficacy of atropine in reducing the rate of myopia progression and increase in axial length among myopic children who were treated with atropine ophthalmic drops ranging from 0.01% to 1% *versus* control based on data from published literature.

Methods

Criteria for considering studies for this review

Types of studies

Randomized controlled trials and prospective interventional controlled trials were considered for inclusion in this review.

Types of participants

Participants of the included studies were pediatric patients aged 4 to 14 years old with myopia on cycloplegic refraction (automated, using either cyclopentolate or tropicamide) regardless of degree.

Types of interventions

Only studies that employed daily topical administration of atropine ophthalmic drops, regardless of concentration, were included. Controls may consist of placebo, alternate treatment, or observation. The study done by Shih *et al.* in 1999[8] used 0.5% tropicamide as control, while in 2001[9] they used multifocal lenses as control. All other studies compared atropine with placebo.

Types of outcome measures

1. Mean difference of rate of myopia progression in diopters per year.
2. Mean difference of increase in axial length in millimeters.

Search methods for identification of studies

Electronic search was done through PubMed, Embase, Google Scholar, Herdin, and Cochrane using free text search and Medical Subject Headings (MeSH) search. Free text search was done through all the above databases up to November 2018. We used the search terms *atropine* and *myopia progression*. Only studies published in English were included in the analysis.

Data collection and analysis

Selection of studies

The studies considered for review were individually screened by two independent reviewers for eligibility. All studies meeting the criteria for eligibility and containing as outcomes either rate of myopia progression or increase in axial length, or both, were included in the analysis. In case of a dispute, this was settled through discussion with a third reviewer.

Data extraction and management

Means and standard deviations for each outcome measure as well as sample sizes for each treatment arm were extracted from each study using a data collection form by a single author. Data was then analyzed using Cochrane's Review Manager 5.3 software. Outcomes were reported as pooled mean difference using the inverse variance method of the random effects model.

Assessment of risk of bias in included studies

The Cochrane Collaboration Risk of Bias Tool for randomized controlled trials was used for the assessment of included studies.[10] Studies were assessed as being "low risk," "high risk," or "unclear" regarding five domains of bias: allocation (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other potential sources of bias.

Measures of treatment effect

Since both outcome measures were dichotomous data that were measured on the same scale across all trials, pooled mean difference (MD) was used to summarize the treatment effect for both rate of myopia progression and increase in axial length. Level of significance was set at alpha = 0.05. Outcomes were reported using the point estimate of the pooled mean difference, its *p*-value, and 95% confidence interval.

Unit of analysis issues

The unit of analysis of each outcome measure was by number of eyes enrolled instead of number of participants. Data for rate of myopia progression and increase in axial length were measured from baseline compared to final measurements.

Multi-arm studies were treated as separate two-arm studies that compared each intervention with control. The multi-arm studies that were treated as separate studies were labeled accordingly using letters.

Myopia progression was expressed in diopters (D)/year. Because myopic refraction is a negative value, a more negative value of myopia progression indicated a higher rate of progression, while a less negative or more positive value indicated a lower rate of progression, which was the beneficial result. For the increase in axial length, values were expressed in millimeters. A lower or more negative value was considered a beneficial result.

Dealing with missing data

Most studies reported complete data including mean, standard deviation, and number of samples for each treatment arm. Only the study by Lee *et al.*[11] did not report the standard deviation for the 0.25% atropine treatment arm. Missing standard deviations were imputed using the correlation coefficient from another study in the meta-analysis, as recommended in the Cochrane Handbook.[12] Studies with imputed standard deviations were subjected to sensitivity analysis.

Assessment of heterogeneity

For each analysis, statistical heterogeneity was computed on each forest plot. Chi-square (I^2) > 50% or its *p*-value ≤ 0.10 was considered as statistically significant heterogeneity of data.

Assessment of reporting biases

Funnel plots of the included studies were generated for each outcome measure. Symmetry and shape of the funnel plots were assessed for publication bias.

Data synthesis

The random effects model was used based on the assumption of heterogeneity of data due to differences in the study populations and treatment concentrations.

Subgroup analysis and investigation of heterogeneity

Planned subgroup analyses were done for each concentration of atropine and each study methodology. For each subgroup analysis, Chi-square (I^2) and its corresponding *p*-value were also computed as described above.

Sensitivity analysis

Sensitivity analysis was done by excluding data from the study with missing standard deviations that were imputed from the correlation coefficient of another study. If treatment effects were the same in the sensitivity analysis, the results of the study were considered robust.

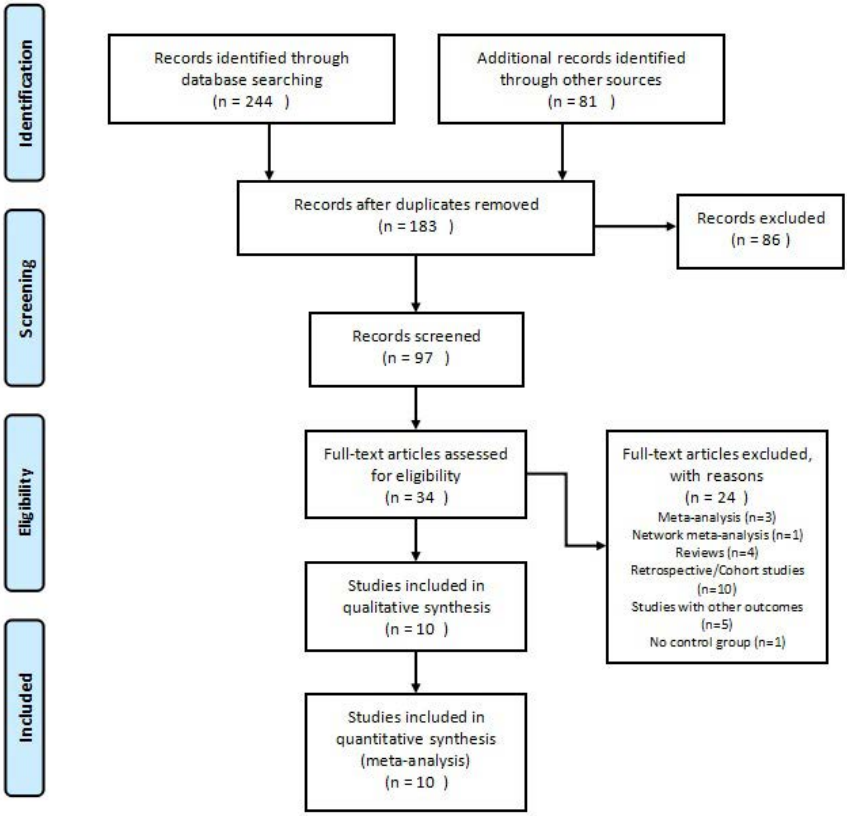

Fig. 1. PRISMA flow diagram of the literature search.

Results

Description of studies

Search results

After a thorough search of the database, 244 studies were retrieved plus an additional 81 studies from other sources. Duplicate reports were removed, resulting in 183 potential relevant studies. Eighty-six reports deemed irrelevant to the objective of this study were excluded. Of the 97 studies screened, 34 full-text articles were assessed for eligibility, of which only ten articles met our inclusion criteria. Eight studies were randomized controlled trials and two were prospective, interventional, non-randomized studies (Fig. 1). Three of the studies had three treatment arms and one had two treatment arms. A total of 1,229 children

Table 1. Characteristics of studies included in the meta-analysis

Study	Country	Type of study	Population (age in years)	Degree of myopia	Intervention	Control	Number of eyes (intervention)	Number of eyes (control)	Outcomes assessed	Follow-up period
Yen (1989)[13]	Taiwan	RCT	6–14	-0.5 to -4.0 D	1% atropine every other day	Placebo (saline)	32	32	Myopic progression	1 year
Shih (1999)[8]	Taiwan	RCT	6–13	-0.5 to -6.75 D	0.5% atropine nightly 0.25% atropine nightly 0.1% atropine nightly	0.5% tropicamide nightly	0.5% atropine: 41 0.25% atropine: 47 0.1% atropine: 49	49	Myopic progression	2 years
Shih (2001)[9]	Taiwan	RCT	6–13	mean baseline myopia -3.28 to -3.34 D	0.5% atropine nightly + multifocal lenses	Multifocal lenses	66	61	Myopic progression, axial length	1.5 years
Chua (2006)[14]	Singapore	RCT	6–12	-1.0 to -6.0 D and < 1.5 D astigmatism	1% atropine daily	Placebo (0.5% hydroxypropyl methylcellulose)	166	190	Myopic progression, axial length	2 years
Fan (2007)[15]	Hong Kong	Interventional non-randomized study	5–10	-3.0 D or more	1% atropine daily	No intervention	23	23	Myopic progression, axial length	1 year
Chia (2012)[7]	Singapore	RCT	6–12	at least -2.0 D and < 1.5 D astigmatism	0.5% atropine nightly 0.1% atropine nightly 0.01% atropine nightly	Placebo (0.5% hydroxypropyl methylcellulose)	0.5% atropine: 139 0.1% atropine: 141 0.01% atropine: 75	190	Myopic progression, axial length	2 years
Yi (2015)[16]	China	RCT	7–12	-1.0 and -6.0 D	1% atropine nightly	Hypromellose + dextran + glycerol (Tears Naturale Free)	62	62	Myopic progression, axial length	1 year
Lee (2016)[11]	Taiwan	Interventional non-randomized study	6–12	less than -3.0 D	0.125% atropine 0.25% atropine	No intervention	0.125% atropine: 32 0.25% atropine: 12	12	Myopic progression	1 year
Wang (2017)[17]	China	RCT	mean: 9.1 (intervention); 8.7 (control)	-0.5 to -2.0 D	0.5% atropine	Hypromellose + dextran + glycerol (Tears Naturale Free)	54	55	Myopic progression	1 year
Yam (2018)[4]	Hong Kong	RCT	4–12	at least -1.0 D and ≤ -2.5 D astigmatism	0.05% atropine nightly 0.025% atropine nightly 0.01% atropine nightly	0.9% sodium chloride	0.05% atropine: 102 0.025% atropine: 91 0.01% atropine: 97	93	Myopic progression, axial length	1 year

D: diopters; RCT: randomized controlled trial

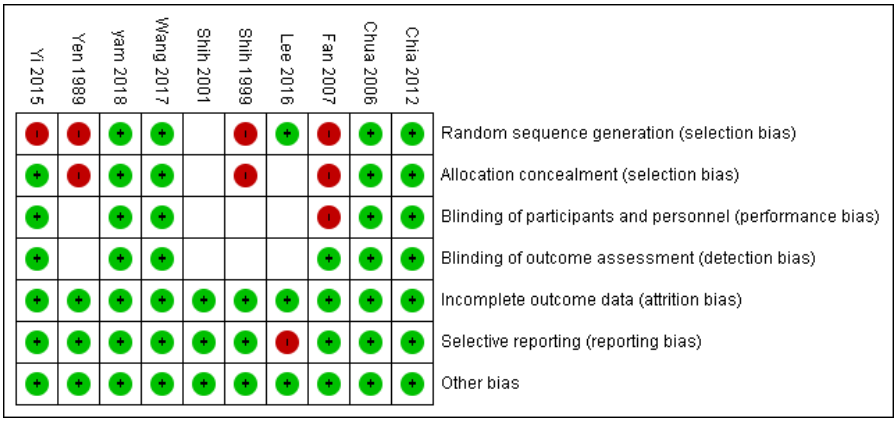

Fig. 2. Summary of risk of bias according to the Cochrane Collaboration Tool.

aged 4 to 14 years were included in this meta-analysis. The baseline cycloplegic refraction (automated, using either cyclopentolate or tropicamide) ranged from -0.5 to -6.75 D and follow-up period was 1 to 2 years. Only six studies had axial length measurement as part of their outcome. The characteristics of studies included are summarized in Table 1.

Risk of bias in included studies

The risk of bias in included studies are summarized in Figure 2. Five[4,7,11,14,17] out of ten included studies described how randomization was done. Methods employed were computer-generated randomization list, draw lots, and stratified random sampling. Studies by Fan *et al.*,[15] Yen *et al.*,[13] and Yi *et al.*,[16] on the other hand, did not elaborate on how the subjects were randomized. Allocation concealment was adequate in most studies and was generally achieved by preparing prepackaged bottles with similar appearance as intervention for different treatment groups or using sequentially numbered opaque sealed envelopes. Approximately 50–60% of the included studies did blinding of participants and outcome assessment as stated in their methodology. Studies by Lee *et al.*,[11] Shih *et al.*,[8,9] and Yen *et al.*[13] did not mention blinding of participants and investigators. Incomplete outcome data were appropriately analyzed. Studies done by Yam *et al.*,[4] Wang *et al.*,[17] Yi *et al.*,[16] Chia *et al.*,[7] and Chua *et al.*[14] used intention-to-treat principle to minimize attrition. All the studies adequately reported the outcomes of interest of the study except for Wang,[17] wherein the results were reported in confidence interval instead of standard deviation.

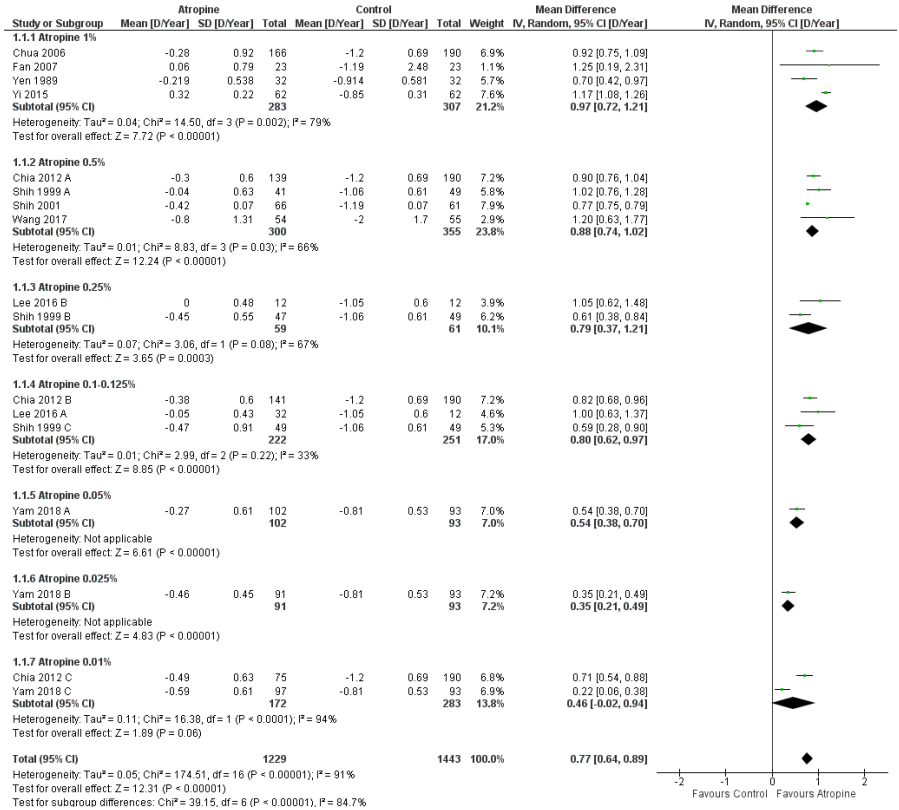

Fig 3. Forest plot of atropine versus control for myopia progression (D/year) with subgroup analysis by concentration.

Effects of interventions

Myopia progression

Meta-analysis of all included studies regardless of atropine concentration using the random effects model yielded a pooled mean difference of 0.77 D/year [CI 0.64, 0.89] between control and atropine for myopia progression (Fig 3). This result shows that, in general, atropine is a favorable intervention for controlling myopia progression in terms of rate of change in refraction. However, heterogeneity was high (I^2 = 91%) across all the studies.

Planned subgroup analysis by concentration showed favorable outcomes for 1%, 0.5%, and 0.1% to 0.125%, 0.05%, and 0.025% concentrations of atropine (Fig 3). The effect showed a decreasing trend with decreasing concentration. The

pooled mean difference of myopia progression from the four studies[13-16] that used 1% atropine was 0.97 D/year [CI 0.72, 1.21], still with significant heterogeneity (I^2 = 79%). For the four studies[7-9,17] that used 0.5% atropine, the pooled mean difference was 0.88 D/year [CI 0.74, 1.02], also with significant heterogeneity (I^2 = 66%). For the two studies[8,11] that used 0.25% atropine, it was 0.79 D/year [0.37, 1.21], with significant heterogeneity (I^2 = 67%). For the three studies[7,8,11] that used 0.1% to 0.125% atropine, the pooled mean difference still favored the intervention at 0.80 D/year [0.62, 0.97], with no significant heterogeneity (I^2 = 33%). There was only one study[4] each for the 0.05% and 0.025% subgroup analyses, precluding meta-analysis of data for those subgroups. Nevertheless, both concentrations of atropine showed favorable outcomes in terms of myopia progression. For the two studies[4,7] in the 0.01% atropine subgroup, the pooled mean difference between atropine and control was 0.46 but the confidence interval [-0.02, 0.94] crossed the midline, indicating that this intervention may or may not be favorable for slowing myopia progression. There was also high heterogeneity within the subgroup (I^2 = 94%) (Fig. 3).

Subgroup analysis by type of study showed that randomized controlled trials favored atropine for decreasing myopia progression, with pooled mean difference of 0.74 D/Year [CI 0.61, 0.86]. This subgroup also had significant heterogeneity (I^2 = 92%). On the other hand, subgroup analysis of nonrandomized controlled trials also favored atropine, with a slightly higher pooled mean difference of 1.04 D/year, a wider confidence interval [CI 0.61, 1.31], and no significant heterogeneity (P = 0.91) (Fig. 4). This subgroup analysis shows that even with nonrandomized

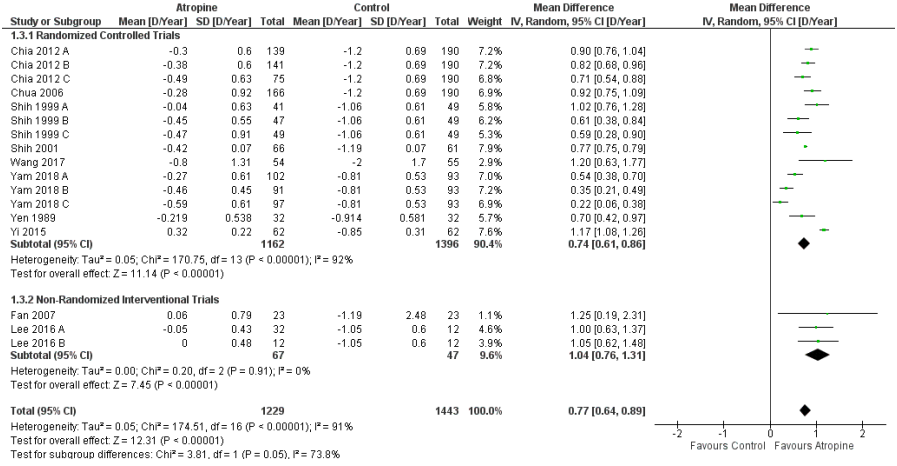

Fig 4. Forest plot of atropine versus control for myopia progression (D/year) with subgroup analysis by study methodology.

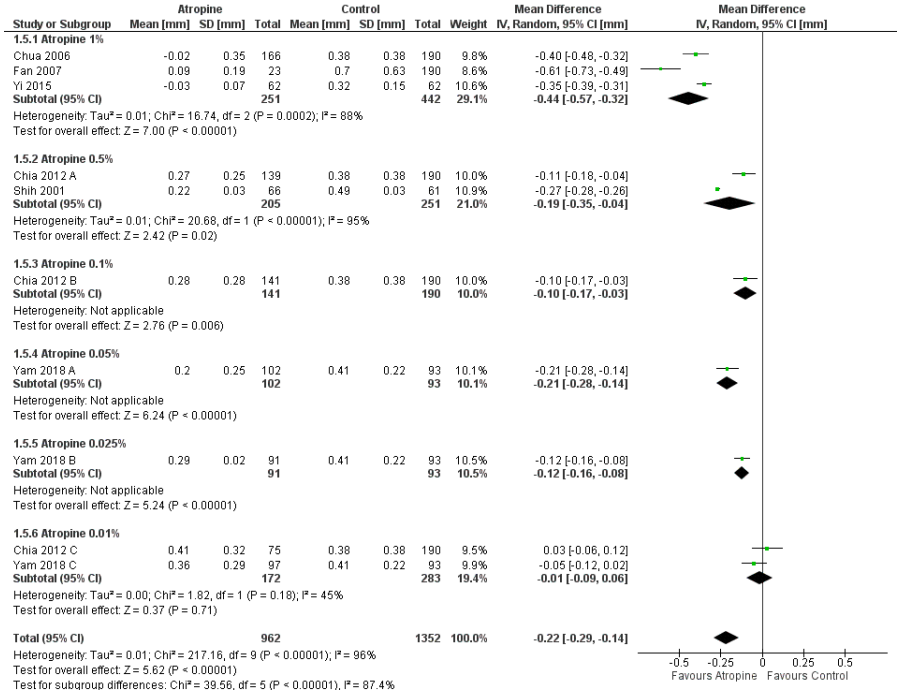

Fig 5. Forest plot of atropine versus control for increase in axial length (mm) with subgroup analysis by concentration.

trials included in the analysis, the results were still robust for retarding myopia progression.

Increase in axial length

For increase in axial length, the overall pooled mean difference between the atropine and control groups was -0.22 mm [CI -0.29, -0.14], which favored atropine. The studies included for this outcome also had high heterogeneity (I^2 = 96%). Subgroup analysis by concentration showed that atropine 1%, 0.5%, 0.1%, 0.05%, and 0.025% had favorable results compared to control for reducing axial elongation, while atropine 0.01% had equivocal results. There was high heterogeneity within the 1% and 0.5% subgroups, while the 0.1%, 0.05%, and 0.025% subgroups only had one study for each analysis. Only the 0.01% subgroup had low heterogeneity (I^2 = 45%). The effects show a decreasing trend with decreasing concentration from 1%, 0.5%, to 0.1%, with pooled mean differences of -0.44 mm [CI -0.57, -0.32], -0.19 mm [CI -0.35, -0.04], and -0.10 mm [CI -0.17, -0.03], respectively. Effects were similar among the 0.5%, 0.1%, 0.05%, and 0.025% subgroups, with pooled mean differences of -0.19 mm [CI -0.35, -0.04], -0.10 mm [CI -0.17, -0.03],

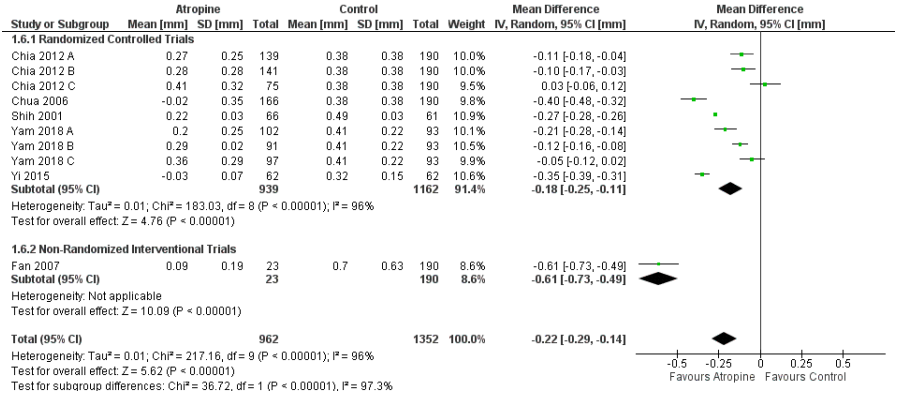

Fig 6. Forest plot of atropine versus control for myopia progression (D/year) with subgroup analysis by study methodology.

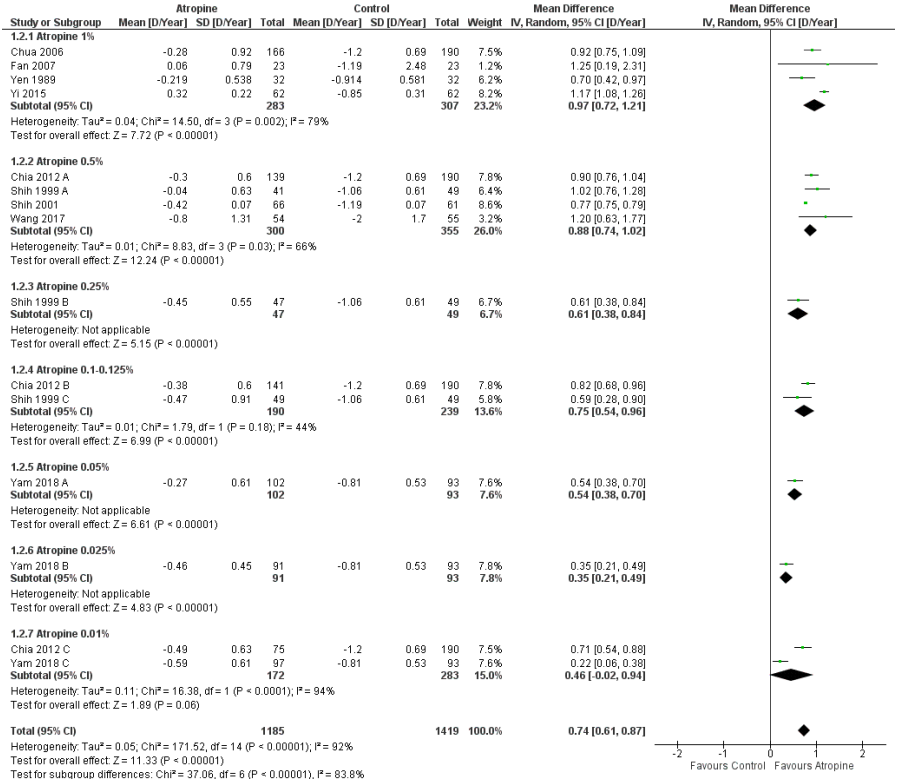

Fig 7. Forest plot of sensitivity analysis for atropine versus control for myopia progression (D/year) with subgroup analysis by concentration.

-0.21 mm [CI -0.28, -0.14], and -0.12 mm [CI -0.16, -0.08], respectively (Fig. 5).

Subgroup analysis by type of study showed that randomized controlled trials favored atropine for decreasing axial elongation, with pooled mean difference of -0.18 mm [C-0.25, -0.11]. This subgroup also had significant heterogeneity (I^2 = 96%). Subgroup analysis of nonrandomized controlled trials only had one remaining study for analysis, which also favored atropine (Fig. 6). This subgroup analysis shows that even with nonrandomized trials included in the analysis, the results were still robust for axial elongation.

Sensitivity analysis

Sensitivity analysis was conducted by excluding data with incomplete and imputed standard deviations from Lee *et al.*[11] for the 0.25% and 0.1–0.125% subgroups. The overall pooled mean difference of 0.74 D/year [CI 0.61, 0.87] on sensitivity analysis was still similar with the original value. The same was true for the sensitivity analysis of the 0.1–0.125% subgroup, with pooled mean difference of 0.75 D/year [CI 0.54, 0.96]. For the 0.25% subgroup, only one study was available for the analysis, which favored atropine (Fig. 7).

Sensitivity analysis of the subgroup analysis by study methodology affected only the subgroup of nonrandomized interventional trials, which had only one remaining study for analysis. The results of the study in this subgroup also favored atropine (Fig. 8).

For the outcome measure increase in axial length, all studies included had complete data and imputation of standard deviation was not done. Hence, sensitivity analysis was not necessary for this outcome.

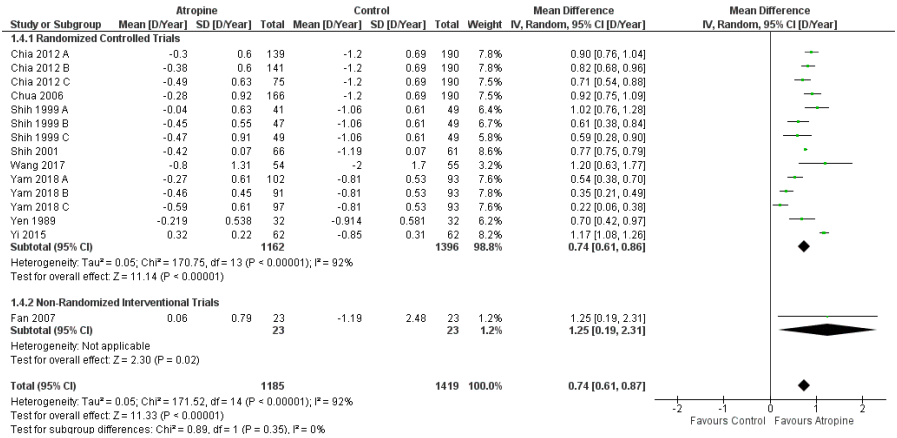

Fig 8. Forest plot of sensitivity analysis for atropine vs control for myopia progression (D/year) with subgroup analysis by study methodology.

Results of the sensitivity analysis showed that the results of the meta-analysis are robust despite inclusion of studies with imputed standard deviations for myopia progression.

Discussion

The results of this meta-analysis show that atropine is effective in reducing myopia progression and decreasing axial elongation. The pooled mean difference is 0.77 D/year for myopia progression, which is similar to previous studies by Song *et al.*[3] and Walline *et al.*[6] Subgroup analysis showed that the effect size decreases as the concentration of atropine decreases, with the 0.01% subgroup having equivocal results. This is consistent with the results of meta-analysis done by Song *et al.*,[3] which showed a dose-response relationship between atropine and myopia progression. However, this study did not have a 0.01% subgroup since low dose atropine was not yet being studied at the time.[3]

Contrary to our results, meta-analyses done by Li *et al.*,[5] Huang *et al.*,[18] and Gong *et al.*[1] all showed no significant difference in slowing myopia progression among various doses of atropine. Li *et al.*[5] analyzed the overall effects only because there were not enough studies for subgroup analysis, and the lowest dose included was 0.025%. Gong *et al.*[1] categorized the different concentrations of atropine as low dose (0.01%), moderate dose (greater than 0.01% to less than 0.5%), and high dose (0.5% to 1.0%). A network meta-analysis by Huang *et al.*[18] also divided the concentration of atropine into low (0.01%), moderate (0.1%), and high dose (0.5% and 1%). The differences in the effects of the value of the lower doses of atropine may not have been delineated because they were arbitrarily clustered together into subgroups.

Results for the increase in axial length also showed that atropine is effective with an overall pooled mean difference of -0.22 mm. However, the 0.01% subgroup likewise showed equivocal results similar to the outcome in myopia progression. The lowest concentration showing efficacy for axial elongation is the 0.025% subgroup. Although our analysis showed positive results, there are still few studies which included axial elongation as their outcome; therefore, more studies are needed to confirm this finding.

Quality of the evidence

Subgroup analysis of studies by methodology showed that conclusions were consistent even when nonrandomized interventional studies were excluded. Further sensitivity analysis showed that the body of evidence was robust in spite of imputed standard deviations from one study. The eight randomized controlled trials and two interventional studies provided adequate evidence to make robust conclusions regarding the objectives.

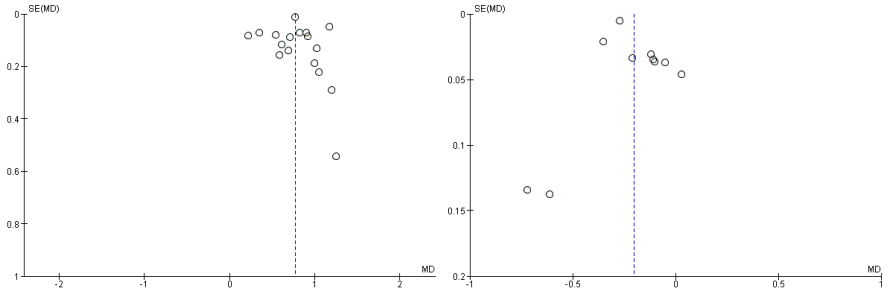

Fig 9. Funnel plots for myopia progression (left) and increase in axial length (right).

Potential biases in the review process

Only articles in English from electronic sources were included in the study. Manual search from offline databases was not done. Only published data from available full-text articles were used. Raw data from authors were not sought in the data collection. Funnel plots for both outcomes (Fig. 9) were asymmetrical with a paucity of small studies, which may indicate publication bias. This asymmetry may also be due to the high heterogeneity of the included studies.

Conclusion

Implications for practice

The use of atropine eyedrops is generally effective for myopic Asian children aged 4 to 14 years old with spherical equivalents of -0.5 D to -6.75 D. Based on current available evidence, the lowest effective dose of atropine in reducing myopic progression and axial elongation is 0.025% atropine daily, but this is based on a single study. The lowest effective concentration for reducing both myopic progression and axial elongation based on more than one study was 0.1–0.125% atropine daily. Pooled results of this meta-analysis showed that 0.01% atropine daily compared to placebo had equivocal results for both outcomes.

Implications for research

More randomized controlled trials are needed to assess the efficacy of low-dose atropine, specifically 0.01%, 0.025% and 0.05%. Only one randomized controlled trial was done for the 0.025% and 0.05% subgroups, while the effect size of the 0.01% subgroup had equivocal results due to lack of statistical difference compared to placebo. Axial elongation should also be included as an outcome measure in all future studies.

Declarations

Ethics approval and consent to participate

This research was submitted to the Institutional Ethics Review Committee of St. Luke's Medical Center Quezon City and was exempted from Ethics Review.

Consent for publication

Not required.

Competing interests

The authors have no proprietary or commercial interest in any materials discussed in this research.

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None to disclose.

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Case Report
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Prominent lymphatic vessel in a functioning bleb after repeat XEN gel stent implantation surgery in pseudoexfoliative glaucoma: a case report

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Abstract
XEN gel stent implantation (XEN) surgery is becoming more popular due to its safety profile and efficacy, with conjunctival lymphatics thought to be critical in maintaining bleb drainage. We are reporting the case of a 75-year-old man with right eye pseudoexfoliative glaucoma who had two previous episodes of failed XEN surgery despite given needling and antimetabolite. He had a repeat XEN surgery in our center and his intraocular pressure was under control at the time of writing without any topical glaucoma medication, needling, nor antimetabolite. On examination, there was presence of prominent, dilated, and irregular lymphatic vessel originating from the distal end of the bleb. Anterior segment optical coherence tomography identified the lymphatic vessel located in the superficial Tenon's layer, which is most likely an initial lymphatic but larger in diameter. This dilated lymphatic vessel may be an important factor for his currently successful filtration surgery.

Keywords: *bleb drainage, conjunctival lymphatics, glaucoma, pseudoexfoliation glaucoma, XEN surgery*

Introduction

Microinvasive glaucoma surgery (MIGS) is becoming more popular due to its safety profile and efficacy. Morgan *et al*. reported that gelatin micro-fistulae implantation had 83% success rate with intraocular pressure (IOP) less than 21 mmHg and reduction of IOP-lowering medications from 3.0 to 0.9 at 6 years follow-up with no significant complications.[1] Similar microfistulae being marketed as XEN gel stent (XEN) with smaller dimension (Allergan, Irvine, CA, USA), is one of the newer modalities to lower IOP by forming a drainage bleb. Conjunctival lymphatics are thought to be critical in maintaining bleb drainage as evidenced by extensive experimental study.[2] It is arguably acceptable to say

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that more dilated and developed lymphatic vessels may have increased aqueous humor drainage, resulting in lower IOP. We are reporting a case of prominent lymphatic vessel in a functioning bleb after repeat XEN surgery.

Case presentation

A 75-year-old man with underlying right eye (RE) pseudoexfoliative glaucoma had XEN implant performed by an external ophthalmologist in 2018 which failed after 2 months due to unknown reasons. It was removed and a second XEN stent was implanted. Unfortunately, despite treatment with needling and 5-fluorouracil injection, the second implant failed and the patient was started back on topical antiglaucoma medication soon after the surgery. The patient was then referred to our institution.

Initial assessment in our institute showed RE visual acuity was 6/6, cornea was clear, conjunctiva was not inflamed with mobile conjunctiva superonasally, pseudophakic, and open angle in all four quadrants on gonioscopy. On gonioscopy, the XEN stent was seen superiorly in the 1 o'clock position entering the ciliary body with the proximal portion angled towards the iris and with the iris plugging the lumen of the XEN, which was considered the cause of failure. The IOP was 14 mmHg with guttae timolol-travoprost and brimonidine-brinzolamide fixed combinations and cup-to-disc ratio (CDR) of 0.7. His left eye (LE) visual acuity was 6/7.5, pseudophakic, IOP of 13 mmHg without any topical antiglaucoma medication, and CDR of 0.4. The patient complained of asymmetrical skin color changes due to topical eyedrops and was keen for surgery. Options and risks regarding XEN stent and glaucoma drainage device were discussed with the patient. The mobile conjunctiva within the superonasal quadrant suggested that little fibrosis had occurred from the prior two XEN stents, thus making this region potentially suitable for reimplantation of XEN. Our usual recommendation in the setting of failed XEN stent is for a glaucoma drainage device given that the usual cause of failure is fibrosis around the stent distal tip. After discussion with the patient regarding the likely outcomes, the patient wished to attempt a third XEN implant, which was performed at our institute. RE ab-interno XEN implant with subconjunctival mitomycin-C 0.01% (5 μg) was performed using eye fixation to free one hand allowing continuous gonioscopy during surgery and reasonably precise localization of the XEN stent through the trabecular meshwork, as previously described.[1] No intraoperative complications occurred.

Postoperative review at week 1 showed superonasal diffuse bleb extending for 3 clock hours with IOP of 9 mmHg. At 1-month, postoperative RE IOP maintained at 10 mmHg with slightly elevated diffuse bleb, as previously noted. In addition, there was a prominent lymphatic vessel noted originating from the distal end of the bleb at approximately 1 o'clock running circumferentially towards the

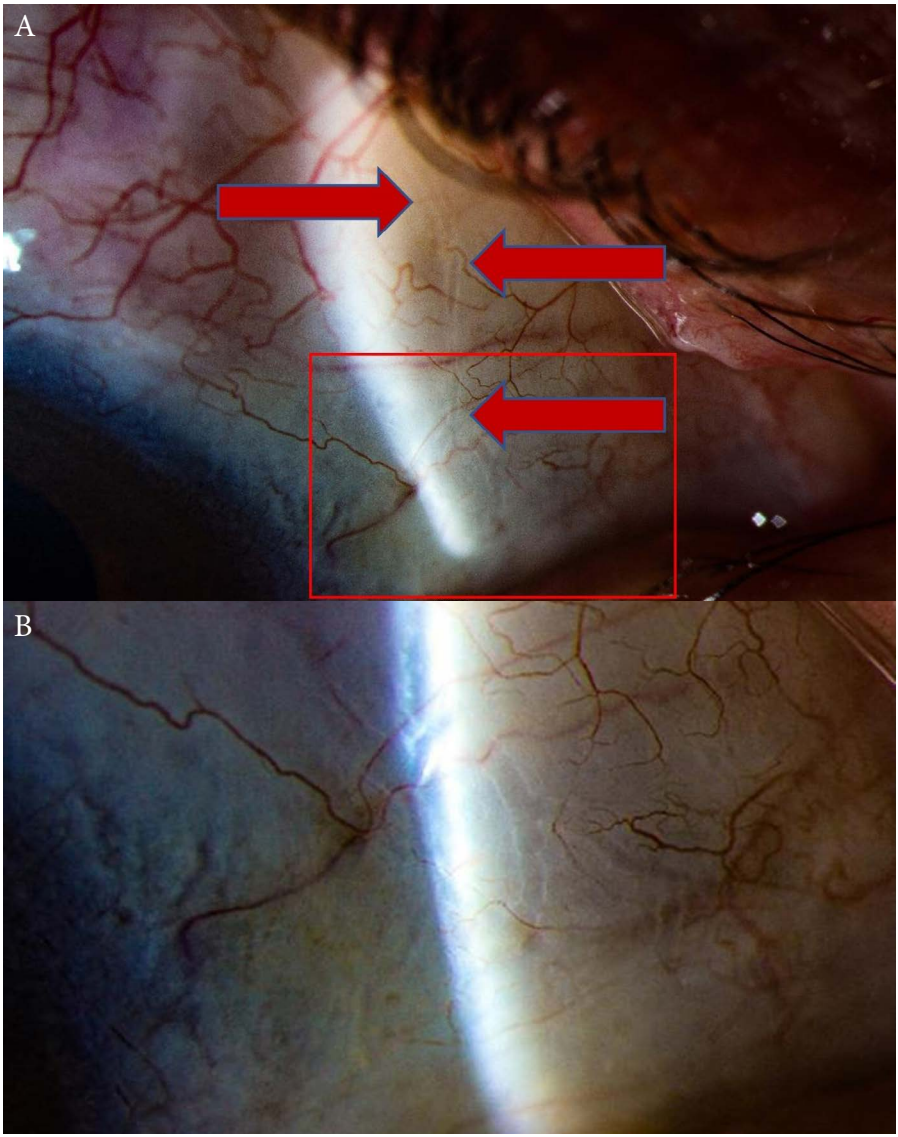

Fig. 1. (A) Prominent and dilated lymphatic vessel (red arrow) captured on slit lamp examination. The lymphatic vessel started superonasally, where the XEN bleb is located, and drained downwards nasally. (B) Magnified area of prominent lymphatic vessel (red square). The vessel with whitish wall and translucent inner segment is clearly demarcated from other blood vessels. The vessel's irregular caliber is clearly noticeable, which further supports that it is likely a lymphatic vessel.

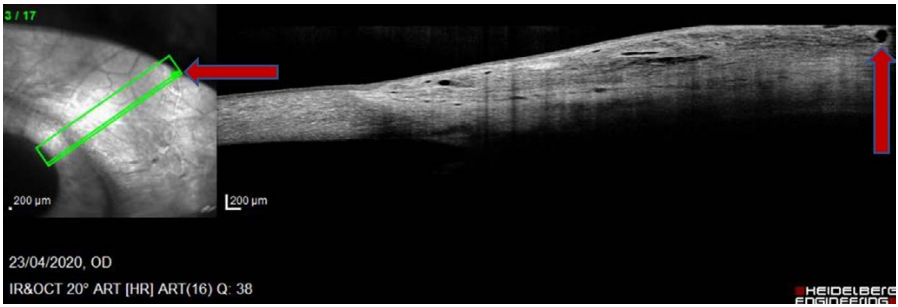

Fig. 2. Anterior segment optical coherence tomography scans of the bleb. The circular lymphatic vessel (red arrow) is located at the superficial Tenon's layer.

inferonasal quadrant (Fig. 1A) at a distance of 3–4 mm from the limbus. Enlarged image also showed the vessel having an irregular caliber (Fig. 1B). This vessel was flat with no cystic dilation and no surrounding chemosis, which tends to occur with lymphangiectasia.[5] Additionally, the vessel was not present prior to surgery. We concluded that this was likely to be a dilated normal lymphatic vessel.

Anterior segment optical coherence tomography identified the lymphatic vessel located in the superficial Tenon's layer (Fig. 2), which was most likely an initial lymphatic vessel. It was well circumscribed, round, and hyporeflective, measuring approximately 111 µm in diameter. Subsequent follow-up at 3 months revealed RE IOP of 13 mmHg without topical antiglaucoma medication. No needling or 5-fluorouracil injection were given after the latest XEN implant.

Discussion

It is postulated that aqueous humor is removed through transconjunctival filtration, reabsorption through walls of degenerated veins, or into aqueous vein or absorption into superficial conjunctival lymphatics.[3] The conjunctival lymphatic network has two layers, initial lymphatics and precollectors. Initial lymphatics are mostly located in the superficial region of Tenon's capsule and are much smaller in caliber. The caliber of the initial lymphatic vessel in our patient was large compared to our initial study on lymphatic and lymphatic capillaries, which are much smaller in caliber.[2] Hence, it was most likely formed after the last XEN implant, allowing aqueous outflow into the superficial Tenon's space and subsequently into this lymphatic vessel, causing its engorgement. It is important to notice that the appearance of the conjunctiva and its blood vessels are almost normal, indicating that there was no significant inflammation and scarring at the site of the bleb.

In our previous experimental study, fluorescein dye was injected into the anterior chamber to determine aqueous humor outflow pathway from the

anterior chamber into subconjunctival tissue, followed by its removal from subconjunctival tissue. A critical role of conjunctival lymphatic drainage in successful outcomes of glaucoma filtration surgery has been demonstrated.[2] Khoo *et al.* found that eyes with lymphatics that connected to drainage trabeculectomy bleb had greater IOP reduction and required fewer eye drops.[4] Similarly, our patient had a prominent dilated lymphatic vessel that developed after surgery and originated from the drainage bleb, which allowed good IOP control. These findings appear more likely to be due to lymphatic dilation rather than conjunctival lymphangiectasia given the time course as well as the lack of chemosis and cystic swelling.[5] Successful filtration surgery depends on consistent aqueous humor outflow pathway from the anterior chamber into conjunctival tissue followed by its removal from the conjunctival tissue. Our patient had two previous episodes of failed XEN implantation despite given needling and antimetabolite. Therefore, he was at risk of failure in further surgery due to fibrosis and scarring, which may occlude the outflow pathway. Despite this, his third XEN implant was still functioning well at the time of writing without further intervention with a noticeable dilated lymphatic vessel.

Conclusion

The patient's dilated lymphatic vessel may be an important factor for his currently successful filtration surgery. However, further study and research is needed on conjunctival lymphatics with regards to physiologic function and relation to IOP control. The photographs contained in this case report illustrate that conjunctival lymphatics can occasionally been seen and that quantification of various lymphatic properties may aid drainage surgery outcomes.

Declarations

Ethics approval and consent to participate

Not required.

Consent for publication

The patient provided informed consent for the use of their clinical data in this case report.

Competing interests

None to disclose.

Funding

None to disclose.

Acknowledgements

None to disclose.

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Case Report
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Ultrasound monitoring for minocycline-induced idiopathic intracranial hypertension

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Abstract

We report a rare case of idiopathic intracranial hypertension following oral minocycline therapy for the treatment of acne. A 29-year-old, non-obese female, with a history of minocycline use for 1 month for treatment of acne presented with headache and transient blurred vision for 3 weeks. She was found to have bilateral disc edema with normal visual acuity and color vision. Magnetic resonance imaging of the brain was normal with partially empty sella features and enlarged tortuous optic nerve in both eyes. Cerebrospinal fluid opening pressure was high. Ultrasound B-scan was done to serially monitor the optic nerve sheath diameter. She improved significantly after stopping the minocycline and following intracranial pressure lowering measures. Idiosyncratic reaction of intracranial hypertension with minocycline can be symptomatic as early as 1 week. Consultants should be aware of this as early consult with ophthalmologists/neurologists can prevent visual loss. A simple ultrasound B-scan can prove to be a vital non-invasive tool in monitoring these patients.

Keywords: *adverse drug reaction, idiopathic intracranial hypertension, minocycline, ultrasound B–scan*

Introduction

Idiopathic intracranial hypertension (IIH), defined by the modified Dandy criteria, is a disorder of unknown etiology characterized by raised intracranial pressure, which can cause severe visual loss if left untreated.[1,2] Certain drugs are implicated in IIH, such as vitamin A, tetracyclines and its derivatives, oral contraceptives, lithium, cyclosporin, etc.[3] The term "idiopathic intracranial hypertension" emphasizes our general lack of understanding of the pathophysiology of this disorder. Therefore, patients who develop a syndrome of raised intracranial pressure secondary to specific medications are still conventionally classified as IIH. Minocycline, the implicated drug in our case, is a tetracycline derivative used in the treatment of acne, malaria, urinary tract infections, etc. We describe a rare

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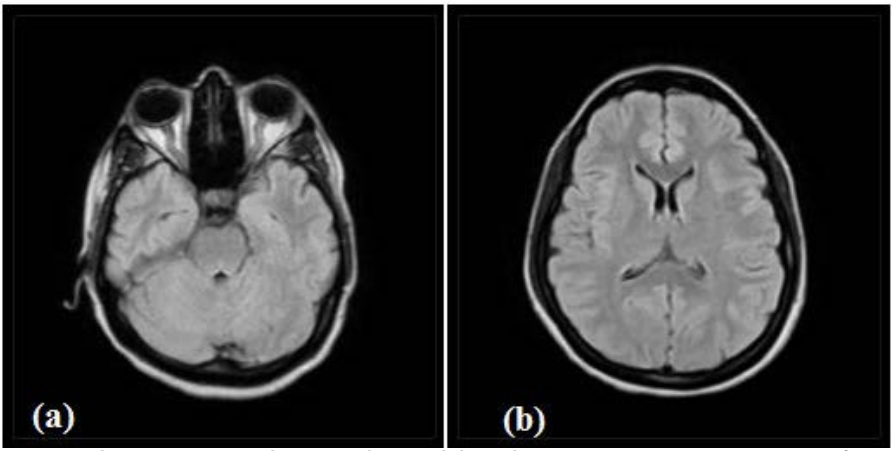

Fig. 1. (a) Flair sequence (axial section) showing bilateral tortuous optic nerves suggestive of raised intracranial tension. (b) Flair sequence (axial section) showing normal study.

case of minocycline-induced IIH and the role of non-invasive ultrasound B-scan in monitoring these patients.

Case presentation

A 29-year-old, non-obese female presented to the Department of Ophthalmology with a history of headache and transient blurred vision for 3 weeks. She also reported to be on treatment for acne with oral minocycline 50 mg once daily for a period of 1 month. There was no history of vomiting, diplopia, or history suggestive of any focal neurological weakness. Systemic examination was within normal limits. On examination, her best-corrected visual acuity was 20/20 with normal near vision (N6) and color vision in both eyes. Anterior segment examination and pupillary reaction were within normal limits. Extraocular movements were full and normal. Dilated fundus evaluation revealed bilateral disc edema suggestive of established papilledema. Disc edema evaluation with neuroimaging showed essentially normal magnetic resonance imaging of the brain with magnetic resonance venogram, bilateral tortuous optic nerves, and partially empty sella, suggesting raised intracranial tension (Fig. 1). The visual field analysis (30-2) showed an enlarged blind spot (Fig. 2). Full blood tests, including erythrocyte sedimentation rate and thyroid profile, were normal. Lumbar puncture for cerebrospinal fluid (CSF) analysis was normal except for a raised opening pressure of 34 cm H_20. Ultrasound B-scan (axial mode) was done to monitor the optic nerve sheath diameter (ONSD), which measured 5.2 mm in the right eye and 5.0 mm in the left eye (Fig. 3).

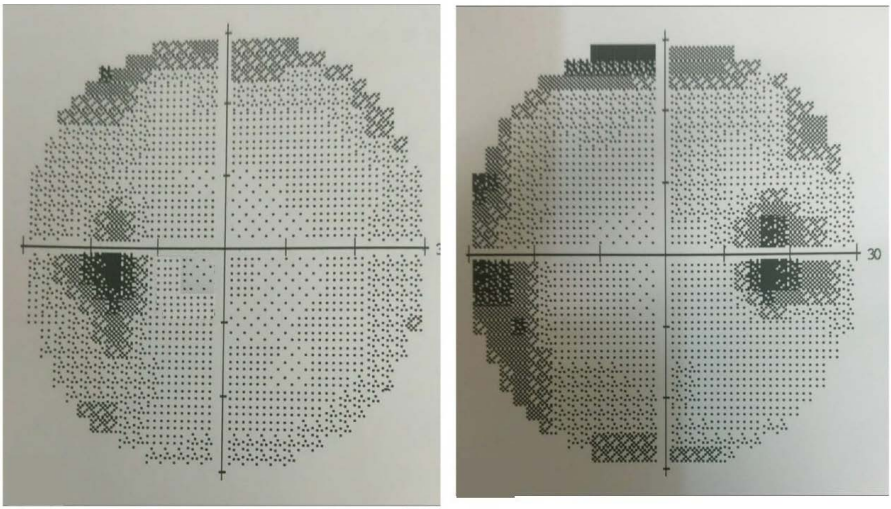

Fig. 2. Visual field analysis showing an enlarged blind spot in both eyes.

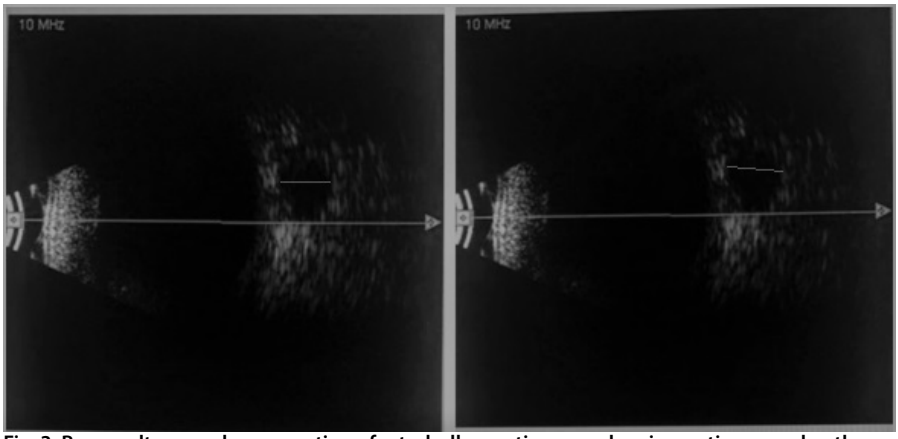

Fig. 3. B-scan ultrasound cross-section of retrobulbar optic nerve showing optic nerve sheath diameter at presentation (5.2 mm in the right eye and 5.1 mm in the left eye).

Diagnosed with IIH, the patient was treated with intravenous mannitol therapy (100 ml thrice daily for 3 days) and subsequently with oral acetazolamide (250 mg twice daily for a week, 250 mg thrice daily in the next week, 500 mg thrice daily for the next 3 weeks, and then tapered over 2 months). Minocycline was discontinued soon upon diagnosis. The patient tolerated oral acetazolamide well with minimal symptoms of gastritis and tingling sensation

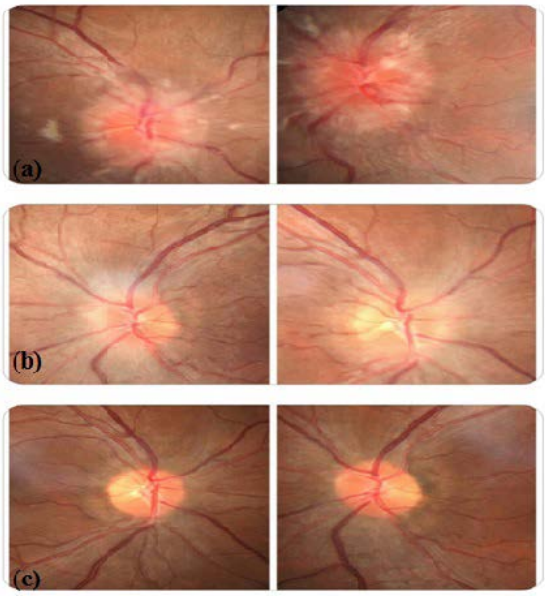

Fig. 4. Disc findings at presentation (a), treatment (b), and after treatment completion (c).

in the upper extremities, which were managed with oral antacid and potassium supplements, respectively. There was significant improvement in the patient's symptoms, with gradual resolution of disc edema over the next 3 weeks on clinical examination (Fig. 4).

Ultrasound B-scan was done serially in axial mode, showing reduction in the ONSD over the following weeks. Clinical resolution of disc edema was seen much later when compared to the ultrasound reduction in diameter. Lumbar puncture procedure was not repeated to measure opening pressure. ONSD was 3.4 mm in the right eye and 3.3 mm in the left eye at the end of 3 months and oral acetazolamide was stopped at that point. The ultrasound B-scan was repeated monthly for the next 3 months and showed no increase of fluid around the optic nerve.

Discussion

IThe term "idiopathic intracranial hypertension" emphasizes our general lack of understanding of the pathophysiology of this disorder.Therefore, patients who develop a syndrome of raised intracranial pressure secondary to specific medications are still conventionally classified as IIH. We applied the Naranjo adverse drug reaction score[4] to our case: the pre-existing case reports, the presence of a

temporal association between the administration of the drug and the onset of the adverse drug reaction (ADR), and the resolution of the pathology following dechallenge, puts this ADR under the "probable" category with a Naranjo score of seven. Rechallenge was not done in our case.

It has been postulated that minocycline reduces CSF absorption at the arachnoid villi, inducing elevated intracranial pressure.[5] The higher lipophilicity of minocycline when compared to other tetracyclines allows greater penetration of the blood-brain barrier, resulting in higher CSF concentrations and perhaps its association with IIH.[6]

The prognosis of IIH after discontinuing the drug is ranges from complete resolution to permanent loss of vision.[7] At 3 months, our patient remained asymptomatic, displayed complete resolution of disc edema, complete visual recovery, and no residual field defect. IIH can present even without papilledema[8] and may need invasive procedures such as lumbar puncture and expensive investigations like magnetic resonance imaging to monitor or detect recurrence. Ultrasonographic ONSD correlates well with severity of papilledema and is very useful in detecting raised intracranial pressure even in the presence of optic atrophy.[9] Being a non-invasive procedure, it was chosen to monitor ONSD in our patient.

The average time lapse between minocycline intake and IIH presentation is variable, ranging from 1 month to 18 months.[10] In the literature, very few cases of minocycline-associated IIH have presented or been symptomatic as early as 1 week. Frasner *et al.*[5] reported a case of a 12-year-old girl who developed fulminant IIH with minocycline. She had a family history of hydrocephalus with ventriculo-peritoneal shunting procedures which may have had some association and precipitated the attack. Our patient had a 1-month history of minocycline intake and became symptomatic with complaints of headache 1 week after initiating the treatment.

Minocycline alone may induce severe IIH with persistently elevated intracranial pressure, and patients with this condition may require medical and surgical treatment beyond discontinuation of the medication.[7] Our patient needed oral acetazolamide therapy for a period of 3 months beyond discontinuation of the drug. There was no recurrence of disc edema and signs of raised intracranial tension as monitored with ONSD using B-scan ultrasonography at the last follow-up 3 months after stopping oral acetazolamide.

Our case suggests minocycline-induced IIH can have an early presentation; timely intervention may prevent visual loss. Ultrasound B-scan is a cheap, non-invasive tool for monitoring these patients.

Conclusion

Idiosyncratic reaction of intracranial hypertension with oral minocycline can be symptomatic and present as early as 1 week after initiating the therapy. Practitioners prescribing the drug should be aware of this potential adverse effect and educate patients about warning symptoms or preferably undertake periodic screening regimens with ophthalmologists for early detection and treatment when symptomatic. B-scan ultrasonography measuring ONSD can be used to detect and monitor these patients with IIH.

Declarations

Ethics approval and consent to participate

None required.

Consent for publication

The patient provided informed consent for the publication of the clinical data contained in this case report.

Competing interests

None to disclose.

Funding

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Acknowledgements

None to disclose.

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