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Efficacy of azithromycin 1% and 1.5% ophthalmic solutions compared to tobramycin 0.3% eye drops: A systematic review and meta-analysis

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Abstract

Background: Azithromycin 1% and 1.5% ophthalmic preparations are used widely in clinical practice for the treatment of signs and symptoms of eye diseases. The aim of this study was to render conclusive evidence by comparing the efficacy of azithromycin 1% and 1.5% over tobramycin 0.3% ophthalmic solutions for the treatment of eye diseases in a short duration in terms of bacterial resolution, the cure rate, and resolving clinical sign and symptoms.

Methods: Systematic searches were performed in the electronic database (MEDLINE, Embase, Emcare, CINAHL, Scopus, PubMed, ProQuest, and Web of Science) and other sources. Multicenter randomized controlled trial studies conducted in English were identified and screened. Analysis of individual studies was conducted using the OpenMeta-analyst and Review Manager Version 5.3 software.

Results: Eleven studies were included in the systematic review and meta-analysis. In clinical cure rate, azithromycin 1% and 1.5% eye drops were more effective than tobramycin 0.3% eye drops in short duration dosing ($\leqslant$5 days) with a twice-a-day regimen (relative risk = 1.13; 95% confidence interval: 1.008, 1.28), whereas on increased duration ($>$5 days), azithromycin is almost similarly as effective as tobramycin (relative risk = 1.007; 95% confidence interval: 0.96, 1.05). There was no significant difference in efficacy of bacterial resolution of azithromycin (1%, 1.5%) eye drops compared to tobramycin (0.3%) eye drops (relative risk = 0.99; 95% confidence interval: 0.96, 1.018). Azithromycin eye drops are effective in improving the signs and symptoms of eye disease.

Conclusion: Azithromycin 1% or 1.5% is more effective in the clinical cure rate of eye disease than tobramycin 0.3% eye drops in $\leqslant$5 days of treatment. It is also the best choice of treatment for improving the signs and symptoms of eye disease. So that we recommend clinicians to use azithromycin 1% or 1.5% eye drops.

Systematic Review Registration: PROSPERO 2019 CRD42019139911

Keywords

Azithromycin, eye diseases, eye drops, tobramycin, efficacy

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Introduction

Azithromycin is an acid-stable orally administered macrolide antimicrobial drug, structurally related to erythromycin, with a similar spectrum of antimicrobial activity.[1] But it is particularly noted for its activity against several gram-negative organisms. Based on in vitro data, azithromycin is more active than erythromycin, clarithromycin, and roxithromycin against *Haemophilus influenzae*. It shows similar activity to erythromycin, clarithromycin, and roxithromycin against *Moraxella catarrhalis* (with good activity against β-lactamase-positive strains of this organism) and *Streptococcus pneumoniae*.[2]

Several clinical trials have proven that a 5-day course of azithromycin administered once a day is equally efficacious to a 7- to 14-day course of other commonly used oral antimicrobials, administered 2–4 times a day, for the treatment of

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upper and lower respiratory tract and skin and skin structure infections. Urethritis and cervicitis caused by chlamydia are treated with a single 1-g dose of azithromycin. Trials have shown azithromycin's adverse-effect profile to be equal or even superior to that of other agents, with only 0.7% of patients discontinuing therapy versus 2.6% for comparable drugs. Azithromycin's primary role in the near future will be in the community setting. Although its use in the hospital may be limited, this drug will be a convenient therapeutic option to have on hand in the emergency room and outpatient clinic. Azithromycin may also be used in the future to treat opportunistic infections in immunocompromised patients.[3]

Azithromycin is recently adapted for topical use in ophthalmology. It is effective against the most frequent pathogens found in bacterial conjunctivitis, gram-positive, and gram-negative bacteria.[4] The clinical efficacy and microbial eradication of 1% and 1.5% azithromycin ophthalmic solutions were found to have comparable results for treatment of different eye diseases like purulent bacterial conjunctivitis,[5,6] Meibomian gland dysfunction, blepharitis,[7] and papulopustular rosacea.[8] Most of the individualized randomized controlled trial (RCT) studies proved that azithromycin ophthalmic solutions are effective for the treatment of the above-mentioned eye diseases when compared with other antibiotics and a different route. Despite individual studies, there have been no conclusive investigations about the efficacy of ophthalmic solution in clinical cure rate and bacterial resolution. Therefore, this study aimed to provide conclusive evidence on the efficacy of azithromycin ophthalmic solutions compared to tobramycin eye drops for the treatment of eye diseases, in terms of clinical cure rate, bacterial resolution, and resolving clinical sign and symptoms of eye diseases.

Materials and methods

Protocol and registration

Study protocol and search strategy. The protocol of this study has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with ID: CRD42019139911. The whole search was conducted by the investigators (B.M.A./lecturer and researcher, T.W./assistant professor). The authors were certified in comprehensive systematic searching techniques and comprehensive systematic review and meta-analysis.

Sources of studies and searching strategies. The systematic searches were conducted from both electronic and other gray literature sources. An electronic database such as MEDLINE (Ovid), Embase (Ovid), Emcare (Ovid), CINAHL (EBSCOhost), Scopus, PubMed, ProQuest, Web of Science, and Cochrane Central Register of Controlled Trials was searched. For unpublished studies and gray literature, WorldCat, Mednar, Google, and Google Scholar were used. Advanced search strategies were applied to each database using search strings, constructed from indexing terms, text words, and key terms of adapting from the review questions. For example, the following search strategy was used on PubMed: efficacy [MeSH] OR "treatment outcome" AND azithromycin [MeSH] OR Tobramycin AND "ophthalmic solution" [MeSH] OR "eye drop." To identify ongoing trials, multiple World Health Organization (WHO) trial registries were searched (see Supplemental Additional File 1). We do not have any regional or time restrictions.

Study selection procedure. We included RCTs and controlled clinical trials that have been conducted in all age groups and written in English, irrespective of duration/time limitation. Studies with abstract only and not able to access the full article were excluded. Observational studies, reviews, commentaries, editorials, case series/reports, and patient stories were not included in the systematic review. Articles extracted from different sources were exported to EndNote X8 citation manager, and duplicates were removed. The authors (B.M.A. and T.W.) screened the title and abstracts of the studies with predefined inclusion criteria independently. These authors also independently collect full texts and evaluate for the eligibility to be included for final analysis by considering study subjects, language, study designs, quality, and outcome. Totally 1509 articles were searched. Of these, 490 articles were screened by title and abstract. After thorough screening, 26 studies were assessed for full. Finally, 11 studies were included in the final analysis (Figure 1). The study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist (see Supplemental Additional File 2).

Description of the outcomes of the systematic review and meta-analysis. Based on our systematic review and meta-analysis questions, we considered three outcome variables to be achieved by the review. The primary outcome variables were clinical cure rate, bacterial resolution, and resolution of clinical signs and symptoms of different eye diseases after treatment by azithromycin ophthalmic solutions in comparison with tobramycin eye drops.

Assessment of methodological quality (risk of bias assessment). The quality assessment (critical appraisal) was performed by the authors (B.M.A. and T.W.) independently using Joanna Briggs Institute (JBI) critical appraisal tool for Randomized Controlled Trials[9] (see Supplemental Additional File 3). The tool has 13 questions. It has yes, no questions, and 1 was given for yes and 0 for no. The scores were summed up and changed to percentages. Studies with $\geqslant$50% were included for the meta-analysis. Special focus was given to clear statement of the objective of the study, the randomness of participant selection, identification of study participants, and preciseness of measurement of outcomes of interest and use of appropriate statistical analysis method, as well as documentation of sources of bias or confounding. The risk of bias in the included studies was assessed using the Cochrane Collaboration's tool for assessing the risk of

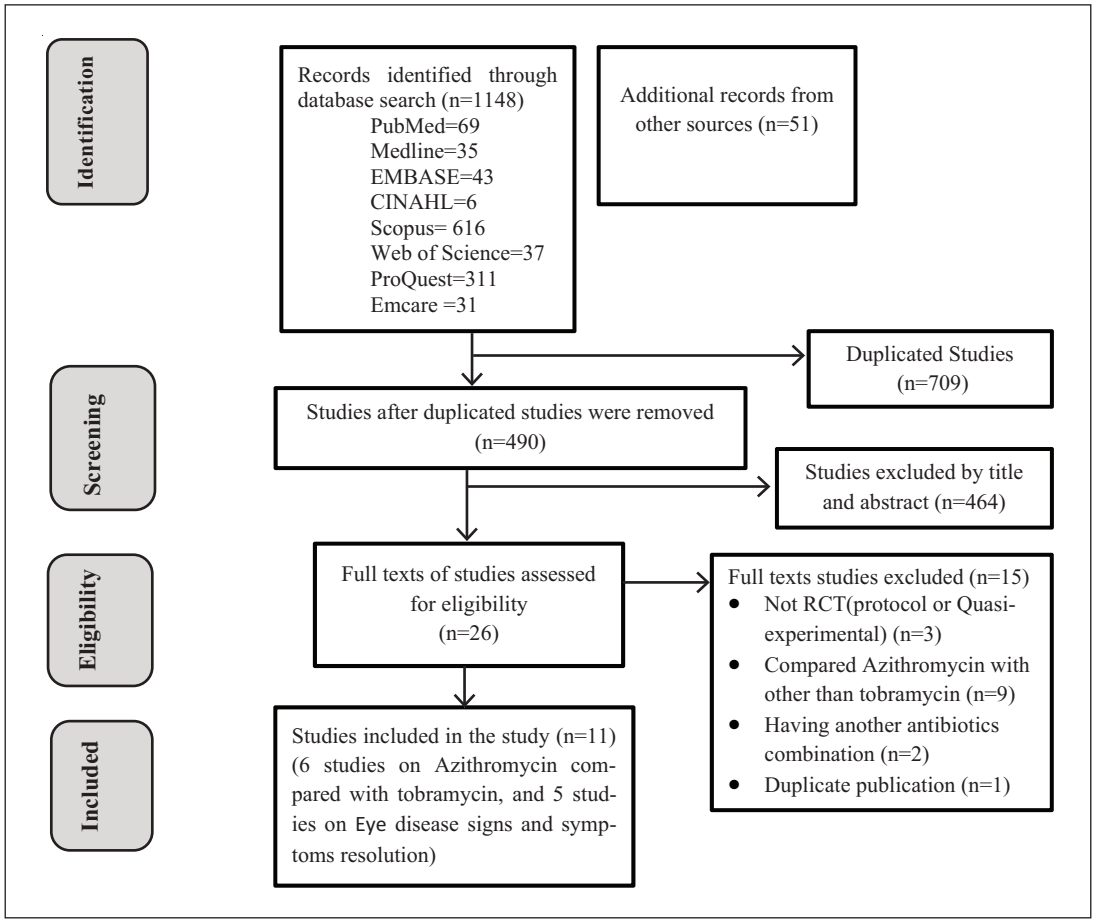

Figure 1. Flow diagram showing the selection process of included studies.

bias in randomized trials[10] (Table 1). During critical appraisal and inclusion of the studies, the discrepancies that arose between the authors were solved by consensus.

Data extraction and recording. Data (containing author, year, the aims of the study, study design, outcome of the study, participants, sample size, interventions, and key findings) were abstracted by using a template prepared in Microsoft Word 2016 (Tables 2 and 3). Of this, the findings (the raw numerical data) of selected studies were extracted by the authors (B.M.A. and T.W.) independently and stored using the data extraction template on Microsoft Excel (2016) spreadsheet.

Strategy for data analysis and assessment of certainty in the findings. Data synthesis and statistical analysis were carried out by the authors (B.M.A. and T.W.). Summary statistics (pooled effect sizes) in relative risk (RR) ratios with 95% confidence intervals (CIs) were calculated for clinical cure rate and bacterial resolution, of azithromycin compared to tobramycin eye drops, using OpenMeta-analyst software. Review manager Version 5.3 software was also used for the standardized mean difference (SMD) of ocular sign and symptom resolution after azithromycin treatment. Forest plots were used to graphically present the meta-analysis results.

The presence of statistical heterogeneity was checked by using the chi-square test (Cochran's Q test) at p value $\leqslant 0.05$. The level of heterogeneity among the studies was quantified using the I^2 statistic described by Higgins and Thompson[18] and p value. A low p value (less than 0.10) or a large I^2 statistic ($I^2 > 75\%$) was considered as evidence of significant heterogeneity. Sensitivity analysis was employed to decrease the heterogeneity. A fixed-effect model was used. Publication bias was explored using visual inspection of the funnel plot. Besides, Egger's regression was carried out to check the symmetry of the funnel plot.[19] Approximately, symmetric funnel plots would indicate a "low risk," whereas asymmetric funnel plots would indicate a "high risk" of publication bias.

Results

A total of 11 RCT studies conducted in different regions of the world were included in this systematic review and meta-analysis. Initially, we got 1199 articles through both electronic databases and other sources. From the identified articles, 709 of them were removed due to duplications, and the remaining 490 articles were screened by title and abstract. Of these, 464 of the studies were excluded since the titles and abstracts did not coincide with our study. The full texts of the 26 studies

Table 1. Risk of bias of included studies.

Author	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Selective reporting (reporting bias)	Blinding (performance bias)	Incomplete outcome data (attrition bias)	Other sources of bias (other bias)	Overall decision on quality of study
Abelson et al.[5]	Low	Low	Low	Low	Low	Low	Low
Bremond-Gignac et al.[6]	Low	Low	Low	Low	Low	Low	Low
Cochereau et al.[11]	Low	Low	Low	Low	Low	Low	Low
Denis et al.[12]	Low	Low	Low	Low	Low	Low	Low
Protzko et al.[13]	Low	Low	Unclear	Low	Low	Low	Moderate
Robert et al.[14]	Low	Low	Low	Low	Low	Low	Low
Bakar Demircay et al.[8]	Low	Unclear	Low	Low	Low	Low	Low
Haque et al.[7]	Low	Low	Low	Low	Low	Low	Low
Luchs[15]	Low	Low	Low	Low	Low	Low	Low
Yildiz et al.[16]	Low	Low	Low	Low	Low	Low	Low
Opitz and Tyler[17]	Low	Low	Low	Low	Low	Low	Low

were reviewed for eligibility and 15 of them were excluded due to inconsistent, incomplete, different outcomes and duplicate publication. Finally, 11 studies were critically appraised for the quality and included in the final analysis. The data were first presented using a narrative synthesis and followed by the meta-analysis result. Summary tables of the included studies were also included (Figure 1, Tables 2 and 3).

The cure rate of azithromycin (1% and 1.5%) compared to tobramycin (0.3%) eye drops

Five multicenter RCTs were included, which was conducted in different countries to compare the clinical efficacy of azithromycin 1% and 1.5% ophthalmic solutions in comparison with tobramycin 0.3% eye drop. All the included studies used 1% and 1.5% azithromycin as the intervention compared with 0.3% tobramycin in the control arms. Two of the five studies reported the clinical cure rate of azithromycin ophthalmic solutions is more effective than tobramycin eye drop.[5,6,11,14] In another way, the rest three studies were reported that there was no significant difference in efficacy.[6,11] This meta-analysis was based on the duration of treatment, which indicated that azithromycin 1% and 1.5% eye drops provide a more rapid clinical cure than tobramycin 0.3% eye drops in a twice-a-day dosing regimen for short duration (⩽5 days) use (RR = 1.13; 95% CI: 1.008, 1.28). Whereas on increased duration (>5 days), azithromycin is as effective as tobramycin (RR = 1.007; 95% CI: 0.96, 1.05; Figure 2).

Bacterial resolution of azithromycin (1%, 1.5%) eye drops compared to tobramycin (0.3%) eye drops

Five of the six RCTs reported the bacterial resolution rate of azithromycin compared to tobramycin eye drops.[5,6,11–13] The overall finding of these studies showed that there is no statistically significant difference in bacterial resolution between azithromycin and tobramycin eye drops (RR = 0.99; 95% CI: 0.96, 1.01).

We also analyzed the effect of duration of treatment on the bacterial resolution rate between these two drugs by subgroup analysis. The result indicates that on short (⩽5 days; RR = 0.99; 95% CI: 0.95, 1.03) and long (>5 days; RR = 0.99; 95% CI: 0.95, 1.02) duration treatments, the bacterial resolution rate of azithromycin eye drops is almost similar with that of tobramycin (Figure 3).

Efficacy of azithromycin ophthalmic solutions (1%, 1.5%) on clinical signs and symptoms

Five RCTs were conducted to evaluate the effects of azithromycin ophthalmic solutions for resolving ocular signs and symptoms due to different eye diseases. Four of the five studies took subjects with blepharitis,[7,15–17] and one study reported the effect of azithromycin on patients with papulopustular rosacea.[8] The efficacy of azithromycin on different clinical signs and symptoms is presented as follows.

Eye symptom scores

All five studies reported the effect of azithromycin ophthalmic solutions on eye symptom scores. The pooled estimate of the studies showed that azithromycin eye drops are effective in improving eye symptom scores with an SMD of −1.42 (95% CI: −1.76, −1.09). The intervention group was in favor of after treatment with an azithromycin eye drop and the control group favors before treatment. Hence, the interpretation is inverse. The finding revealed there was significant statistical heterogeneity ($I^2 = 82\%$, $\chi^2 = 22$, $p = 0.0002$; Figure 4).

Eyelid finding scores

Four of the studies [8,7,16,17] reported the clinical efficacy of azithromycin ophthalmic solutions in improving eyelid finding scores. The SMD of these studies indicates that there is a statistically significant improvement in the severity of eyelid finding scores with an SMD of −1.94 (95% CI: −2.36, −1.52)

Table 2. Descriptions of included studies for evaluating the efficacy of azithromycin as compared to tobramycin eye drops.

Study description of included studies					
Author, country	Aim of the study	Study design/outcome/ participants	Sample size	Interventions	Key finding
Abelson et al.,[5] USA	To evaluate the efficacy of an ophthalmic formulation of 1% azithromycin and demonstrate equivalence with 0.3% tobramycin ophthalmic solution	Prospective, randomized, active-controlled, double-masked, phase 3 trial/the efficacy of 1% azithromycin compared to tobramycin/ bacteriologically confirmed participants	CR I = 159 C = 157 T = 316 BR I = 159 C = 157 T = 316	IG: Participants received 1% azithromycin for 5 days CG: Participants received tobramycin 0.3% ophthalmic solution	CR: 127/159 CR: 123/157 BR:140/159 BR: 148/157
Bremond-Gignac et al.,[6] France, Germany, Italy, Poland, Portugal, Romania, Algeria, and Tunisia	To determine the efficacy and safety of azithromycin 1.5% eye drops in a pediatric population with purulent bacterial conjunctivitis	Multicentre, international, RCT/efficacy and safety of azithromycin/children (from 1 day to 18 years old) with purulent bacterial conjunctivitis, defined by mild to severe bulbar conjunctival injection and purulent discharge in at least one eye	CR I = 102 C = 101 T = 203 BR I = 102 C = 101 T = 203	IG: Azithromycin 1.5% eye drops (one drop twice daily) CG: Tobramycin 0.3% eye drops regimen (every 2 h for 2 days, then 4 times daily for 5 days)	Day 3 CR: 48/102 CR: 29/101 Day 7 CR: 91/102 CR: 79/101 Day 7 BR: 85/102 BR: 80/101
Cochereau et al.,[11] France, India, Bulgaria, Guinea Conakry, Morocco, Portugal, Romania, and Tunisia	To compare the efficacy and safety of azithromycin 1.5% eye drops, for 3 days with tobramycin 0.3% for 7 days to treat purulent bacterial conjunctivitis	Multicenter, investigator-masked RCT/efficacy of azithromycin 1.5% for 3 days compared to tobramycin for 7 days/children and adults with purulent bacterial conjunctivitis	CR I = 245 C = 226 T = 471 BR Day 3 I = 237 C = 216 T = 453 Day 9 I = 236 C = 223 T = 459	IG: Participants received either azithromycin 1.5% twice daily for 3 days CG: Tobramycin 0.3%, one drop every 2 h for 2 days, then 4 times daily for 5 days	Day 9 CR: 215/245 CR: 202/226 BR Day 3 BR: 202/237 BR: 181/216 Day 9 BR: 219/236 BR: 211/223
Denis et al.,[12] France, Bulgaria, Guinea Conakry, India, Morocco, Portugal, Romania, and Tunisia	To compare antibacterial efficacy of topically applied azithromycin 1.5% with tobramycin 0.3% in a multicenter, randomized, investigator-masked study for the treatment of purulent bacterial conjunctivitis	Multicenter, investigator-masked RCT/BR of topical therapy with azithromycin 1.5%/children, adult, infant, and newborn patients at least 1 day of age and diagnosed with purulent bacterial conjunctivitis	BR Day 3 I = 237 C = 216 T = 453 Day 9 I = 236 C = 223 T = 459	IG: Azithromycin 1.5% eye drops, one drop twice daily for 3 days CG: Tobramycin 0.3% eye drops, one drop every 2 h while awake up to 8 times a day for 2 days, then one drop 4 times daily for 5 days.	BR Day 3 BR: 204/239 BR: 183/218 Day 9 BR: 221/238 BR: 213/225
Protzko et al.,[13] USA	To compare the safety and tolerability of 1.0% azithromycin in a polymeric mucoadhesive delivery system with 0.3% tobramycin ophthalmic solution for the treatment of bacterial conjunctivitis	Prospective, randomized, active-controlled, double-masked, phase 3 trial/safety, efficacy, and tolerability of 1% azithromycin/subjects with a clinical diagnosis of bacterial conjunctivitis at 47 sites	I = 159 C = 157 T = 316	IG: 1% Azithromycin twice a day on days 1 and 2 and daily on days 3–5 CG: 0.3% Tobramycin	Bacterial eradication rate Day 5 BR: 147/159 BR: 147/157
Robert et al.,[14] France	To compare the clinical efficacy (signs and symptoms) and safety of azithromycin 1.5% eye drops with tobramycin 0.3%.	Multicenter, investigator-masked RCT/efficacy and safety of 1.5% azithromycin compared to 0.3% tobramycin/ patients with purulent bacterial conjunctivitis	CR I = 245 C = 226 T = 471	IG: Azithromycin 1.5% twice daily for 3 days CG: Patients received tobramycin 0.3%, one drop every 2 h for 2 days, then 4 times daily for 5 days	Clinical CR Day 9 CR: 216/246 CR: 203/227

BR: bacterial resolution; C: control; CG: control group; CR: cure rate; I: intervention; IG: intervention group; T: total; RCT: randomized control trial.

Table 3. Descriptions of included studies for clinical sign and symptoms of eye disease.

Author	Eye symptom scores		Eyelid finding scores		Conjunctival hyperemia		Schirmer test (mm)		Meibomian gland secretion		TBUT (sc)		Ocular surface staining scores	
	Before Mean ± SD (median)	After Mean ± SD (median)	Before Mean ± SD (median)	After Mean ± SD (median)	Before Mean ± SD (median)	After Mean ± SD (median)	Before Mean ± SD (median)	After Mean ± SD (median)	Before Mean ± SD (median)	After Mean ± SD (median)	Before Mean ± SD (median)	After Mean ± SD (median)	Before Mean ± SD (median)	After Mean ± SD (median)
Bakar et al.[8]	2.22 ± 1.98 (2.00)	0.28 ± 0.15 (0.00)	2.72 ± 1.01 (3.00)	1.44 ± 0.98 (1.00)	1.39 ± 0.60 (1.00)	0.94 ± 0.72 (1.00)	19.11 ± 7.98 (20.0)	23.72 ± 8.09 (25.0)			7.78 ± 3.52 (8.00)	9.06 ± 2.41 (10.5)	0.88 ± 0.90 (1.00)	0.88 ± 0.83 (0.00)
Haque et al.[7]	2.22 ± 0.72 (2.00)	0.82 ± 0.96 (0.0)	2.0 (0.00) 2.0	1.2 (0.47) 1.0	1.8 (0.50) 2.0	1.3 (0.56) 1.0					1.88 ± 0.57 (1.76)	1.64 ± 0.73 (1.39)	1.36 ± 0.66 (1.00)	1.3 ± 0.57 (1.00)
Luchs[15]	3.2 ± 0.65	1.1 ± 0.64	1.97 ± 0.77	0.67 ± 0.61					2.5 ± 0.92	0.8 ± 0.43				
Yildiz et al.[16]	2.33 ± 0.49	0.62 ± 0.65	2.20 ± 0.56	0.61 ± 0.65	1.80 ± 0.56	0.47 ± 0.52	17.73 ± 3.56	20.46 ± 1.98	2.13 ± 0.64	0.54 ± 0.52	7.87 ± 1.51	8.39 ± 1.26	1.60 ± 0.51	1.00 ± 0.58
Opitz and Tyler[17]	2.73 ± 0.89	2.21 ± 0.78					11.54 ± 7.33	14.31 ± 9.53	2.44 ± 0.65	1.62 ± 0.57	4.37 ± 1.67	6.58 ± 2.84	3.65 ± 3.06	0.62 ± 0.80

TBUT (sc): the tear breakup time in seconds; SD: standard deviation.

The intervention group was in favor of after treatment with an azithromycin eye drop and the control group favors before treatment. Hence, the interpretation is inverse (Figure 5).

Meibomian gland secretion

Blepharitis, Meibomian gland dysfunction, and other ocular diseases lead to dry eye due to decreased secretions.[20–22] Three RCTs[6,15,16] were found to report the effect of azithromycin on improving Meibomian gland secretion. The pooled estimate of the studies revealed that patients treated with azithromycin showed statistically significant improvement in Meibomian gland secretion with an SMD of −1.78 (95% CI: −2.25, −1.30). The intervention group was in favor of after treatment with an azithromycin eye drop and the control group favors before treatment. Hence, the interpretation is inverse (Figure 6).

Ocular surface staining scores

Fluorescein and rose bengal dyes have been reported to be advantageous for measuring ocular surface staining scores.[23] Four studies[8,7,16,17] evaluated the efficacy of azithromycin ophthalmic solutions on ocular surface staining scores, and the overall result indicated that azithromycin is effective in improving the staining scores due to some eye disease with an SMD of −0.57 (95% CI: −0.88, −0.25; Figure 7).

Tear breakup time in seconds

The tear breakup time (TBUT) is recorded as the number of seconds that elapse between the last blink and the appearance of the first dry spot in the tear film. A TBUT under 10 s is considered abnormal.[24] The overall effect of azithromycin treatment from four RCTs showed that TBUT was not significantly improved with the SMD of 0.31 (95% CI: 0.00, 0.62; Figure 8).

Schirmer test in millimeters

The Schirmer test has been widely used for the assessment of the adequacy of tear production. This test is used when a person experiences very dry eyes or excessive watering of the eyes.[25] Results from three RCT studies showed that there is an increase in the Schirmer test value after study subjects are treated with azithromycin eye drops. The pooled estimate of these studies is inconsistent with individual studies with an SMD of 0.54 (95% CI: 0.17, 0.91; Figure 9).

Conjunctival hyperemia

Conjunctival hyperemia is dilation and redness of the conjunctival blood vessels secondary to eye diseases. The outline of hyperemia often appears with the greatest redness at the fornices and declines moving toward the limbus.[26] Three studies[8,7,16] reported the effect of azithromycin eye drops for conjunctival

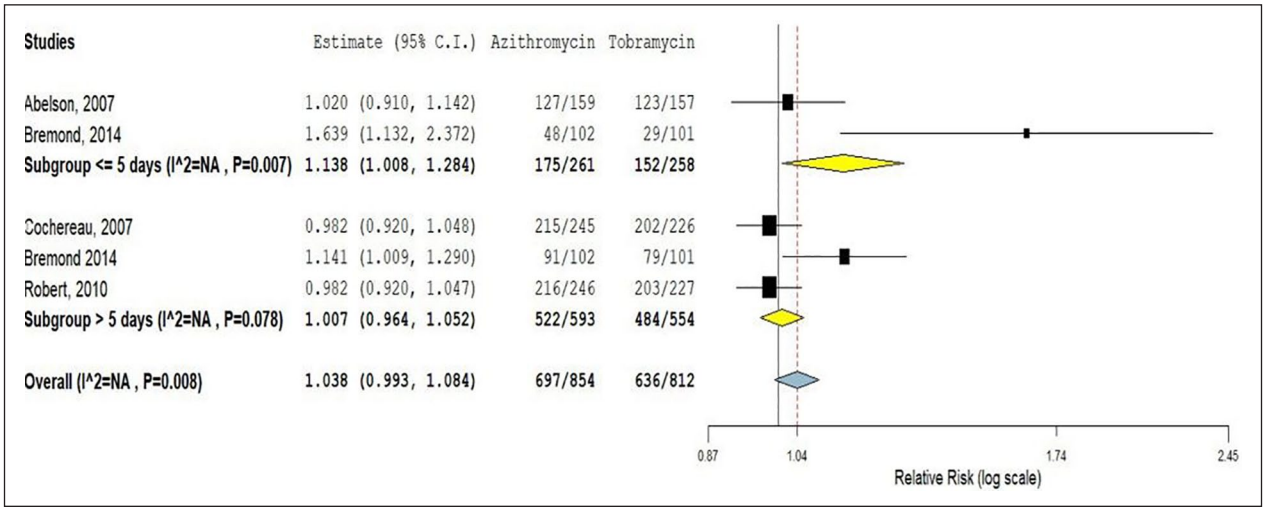

Figure 2. Clinical cure rate of azithromycin ophthalmic solutions compared to tobramycin eye drop.

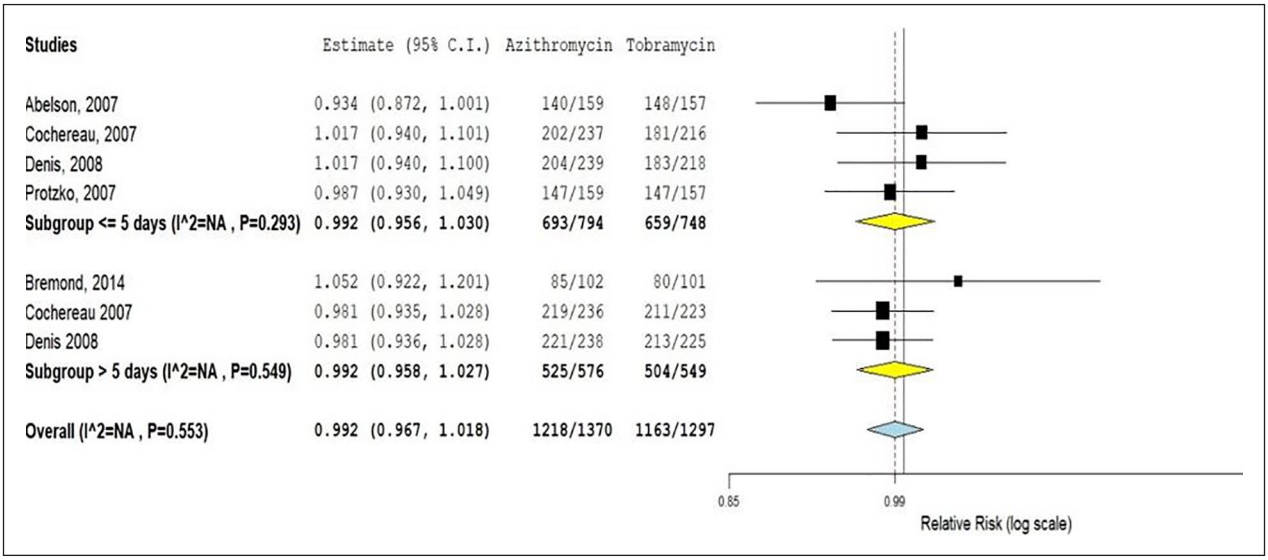

Figure 3. Bacterial resolution rate of azithromycin ophthalmic solutions compared to tobramycin eye drop.

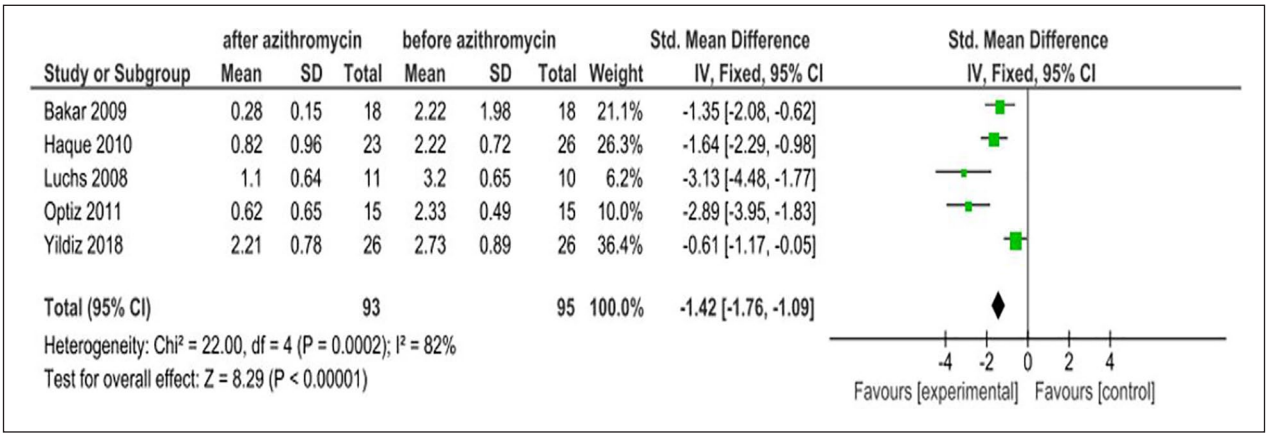

Figure 4. Effect of azithromycin eye drops (1%, 1.5%) on eye symptom scores.

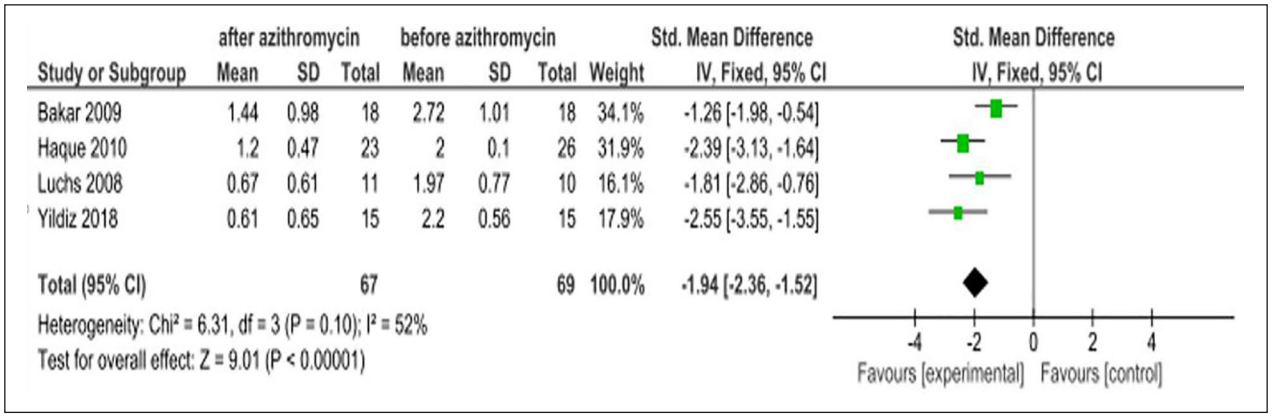

Figure 5. Effect of azithromycin eye drops (1%, 1.5%) on eyelid finding scores.

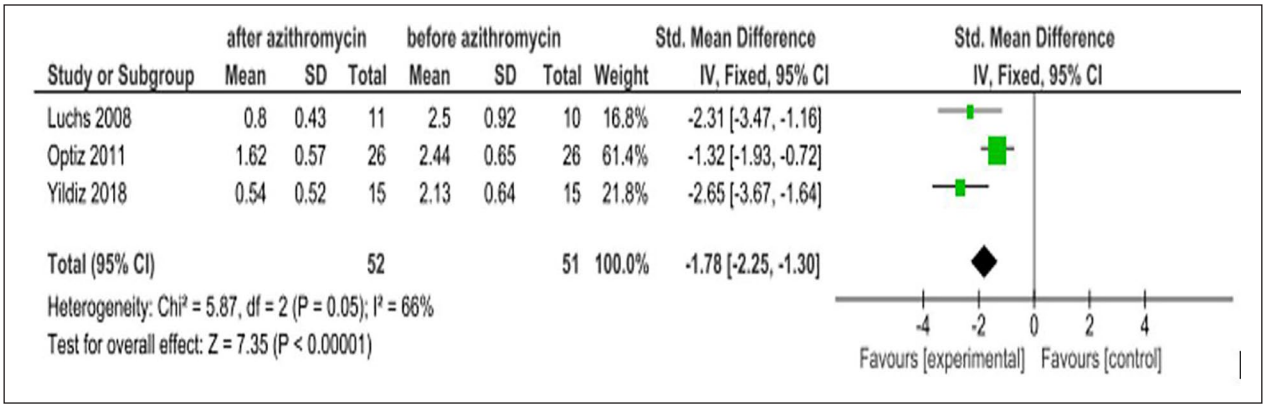

Figure 6. Effect of azithromycin eye drops (1%, 1.5%) on Meibomian gland secretion.

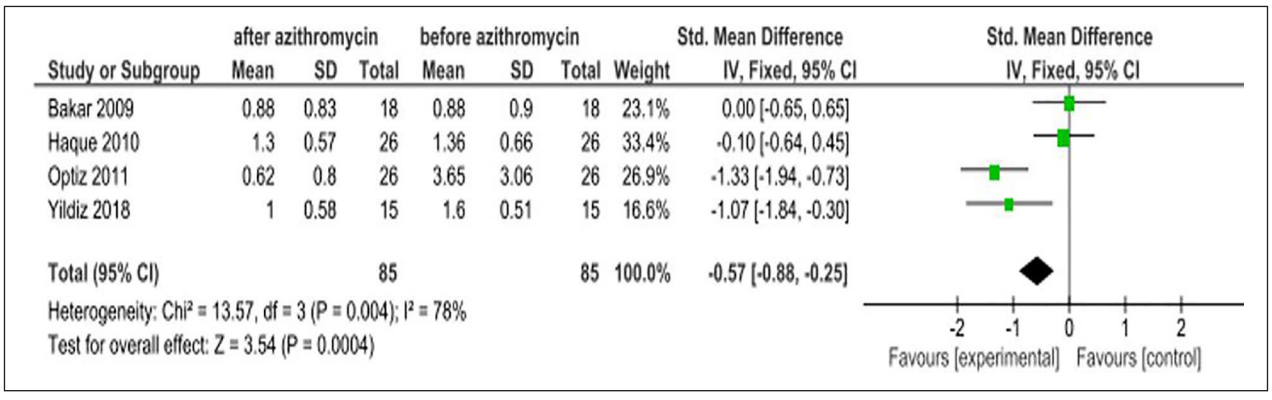

Figure 7. Effect of azithromycin eye drops (1%, 1.5%) on ocular surface staining scores.

hyperemia due to different eye diseases. The pooled estimate of these studies indicates azithromycin ophthalmic solutions were effective in decreasing conjunctival hyperemia with an SMD of −1.09 (95% CI: −1.49, −0.69; Figure 10).

Discussion

This systemic review and meta-analysis presented the concluded evidence on the efficacy of azithromycin ophthalmic solutions for the treatment of eye diseases compared to tobramycin eye drops in terms of clinical cure rate, bacterial resolution, and resolving clinical sign and symptoms of eye diseases by summarizing primary RCTs. A total of 11 studies that have been critically appraised using the JBI assessment checklist, undertaken in different countries in the world, were identified and included. Even though we identified and included similar studies, the duration of the drug and its efficacy were different, we performed subgroup

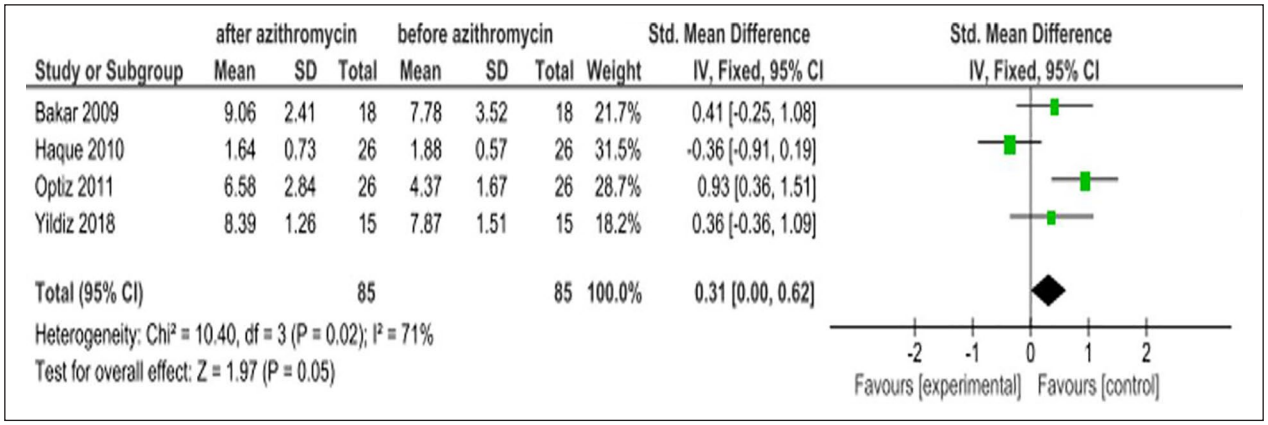

Figure 8. Effect of azithromycin eye drops (1%, 1.5%) on TBUT.

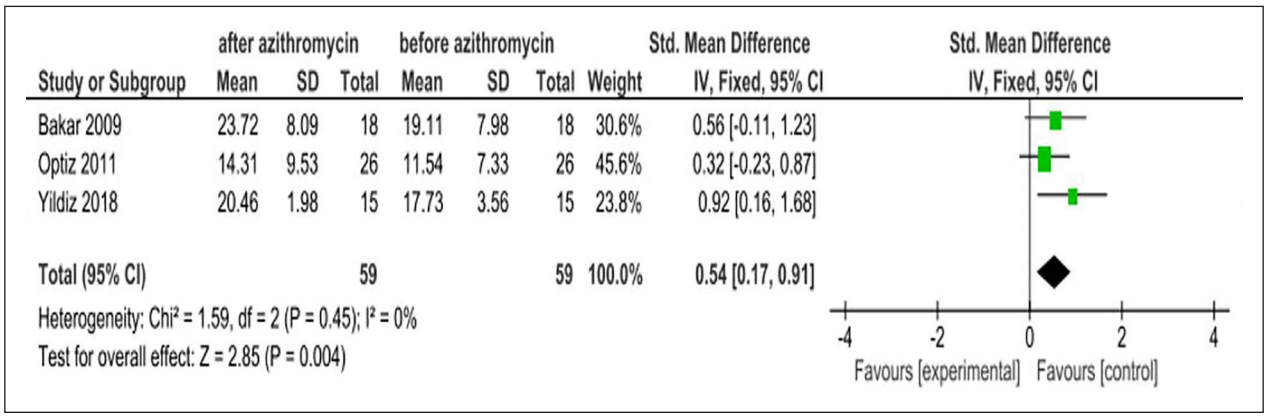

Figure 9. Effect of azithromycin eye drops (1%, 1.5%) on Schirmer test in millimeters.

analysis. The studies conducted in a non-English language and incomplete abstract were excluded.

This study infers that azithromycin ophthalmic solution is a better treatment choice than tobramycin eye drop to rapidly improving eye diseases, mainly in less than or equal to 5-day treatment for 2 times or more dosing per day. The finding is supported by a multicenter, international, randomized, investigator-masked study which declared azithromycin was superior to tobramycin in clinical cure rate on day 3.[6] Similarly, it is also consistent with a study done on the microbiologic efficacy of 3-day treatment with azithromycin 1.5% eye drops for purulent bacterial conjunctivitis.[12]

Similarly, many studies clearly show azithromycin 1.5% for 3 days (six drops) was as effective and safe as tobramycin for 7 days (36 drops).[11,13,14] The azithromycin 1.5% regimen produced a rapid resolution of cardinal signs of purulent bacterial conjunctivitis with a more convenient dosage regimen. Such improved convenience is likely to improve compliance and lessen the burden of illness for patients and carers.[27] More azithromycin than tobramycin patients presented an early clinical cure at day 3. Due to its twice-daily dosing regimen for 3 days, azithromycin represents a step forward in the management of purulent bacterial conjunctivitis, especially in children. This new anti-infective product has the advantage of a short treatment course which could lead to an improvement in patient compliance.[6,11,12] Azithromycin 1% is safe and can be administered in a regimen of less frequent doses than can tobramycin.[14]

However, it is contradicted by a randomized trial study, which was reported that bacterial eradication was lower in the 1% azithromycin eye drop treatment group than in the tobramycin group.[5] Despite this, most of the studies were on the support of the efficacy of the azithromycin eye drop in the clinical cure rate in short durations over tobramycin eye drop.

The azithromycin 1.5% regimen produced a rapid resolution of cardinal signs and symptoms of eye disease. Significant improvement was verified on the eye symptom scores,[8,7,15] eyelid finding scores, Meibomian gland secretion,[8,7,16] ocular surface staining scores,[7,8,16] TBUT in seconds,[7,8,16] Schirmer test in millimeters,8,16 and conjunctival hyperemia[8,7,16] with less than 5-day azithromycin ophthalmic solution treatment.

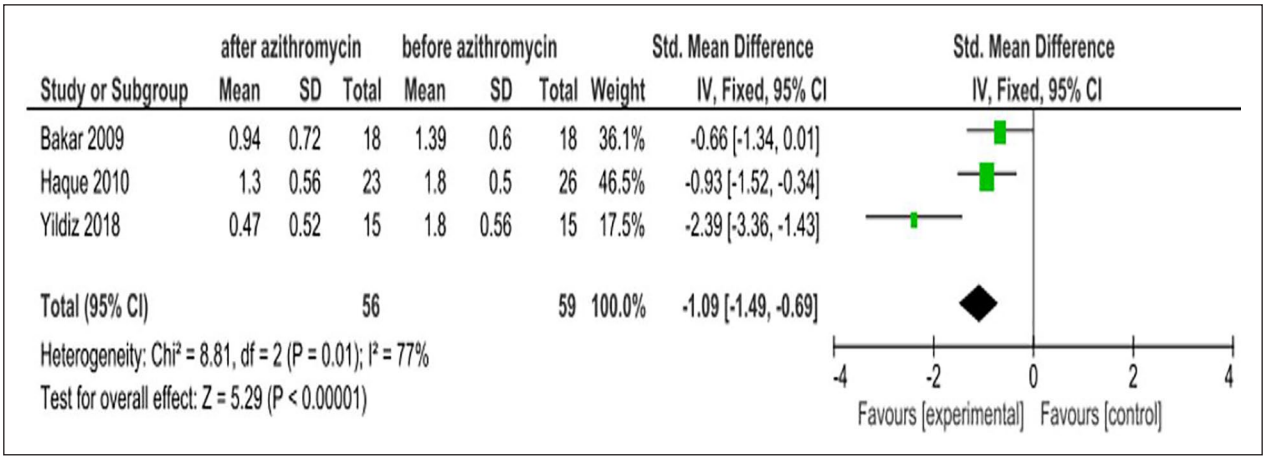

Figure 10. Effect of azithromycin eye drops (1%, 1.5%) on reducing conjunctival hyperemia.

Conclusion

Azithromycin 1% and 1.5% is as effective as tobramycin 0.3% in the clinical cure rate for less than 5 days of treatment. It is also the best choice of treatment for improving the signs and symptoms of eye disease: eye symptom scores, eyelid finding scores, Meibomian gland secretion, ocular surface staining scores, and conjunctival hyperemia. It is the safest drug for topical use. In addition, azithromycin has longer ocular drug residence time, less frequent dosing, and an increase in patient compliance. Therefore, this makes azithromycin the most ideal topical antibiotic over tobramycin eye drops to get a good result in a short duration. So that we recommend clinicians to use azithromycin 1% or 1.5% eye drops for the treatments of eye diseases to get good results.

Strengths and limitations

The strength of this study is that the included studies are RCTs conducted in different contexts and settings. The strengths of this meta-analysis include a broad literature search, screening and data extraction performed in duplicate, careful exclusion of studies with overlapping populations, and the final summary result depends on critically appraised studies. The limitations of this systematic review and meta-analysis is it did not include studies conducted in languages other than English. In addition, the included studies have significant heterogeneity, which was due to the variation between studies in characteristics of the study population, medical and nonmedical factors as a reason for the variation between studies.

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Author contributions

B.M.A. and T.W. conceived and designed the review. Both authors carried out the draft of the manuscript; developed the search strings; screened and selected studies; carried out analysis and interpretation; rigorously reviewed the manuscript; and read and approved the final version of the manuscript. B.M.A. is the guarantor of the review.

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Supplemental material

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