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

CURRENT STATUS: POSTED

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DOI: 10.21203/rs.2.22169/v1

SUBJECT AREAS
  Toxicology    Clinical Pharmacology

KEYWORDS
  Azithromycin, Tobramycin, Efficacy, Eye drops, Eye diseases
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. Despite individual studies, there have been no summarized evidence about the efficacy of azithromycin over tobramycin eye drops. Therefore, the aim of this study was to abridge this gap by rendering 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 short duration in terms of bacterial resolution, cure rate and resolving clinical sign and symptoms of eye diseases.

Methods: Systematic searches were performed in both electronic (Medline (Ovid), EMBASE (Ovid), Emcare (Ovid), CINAHL (EBSCOhost), Scopus, PubMed, ProQuest, Web of Science and Cochrane Central Register of Controlled Trials) and other sources (Worldcat, Mednar, Google and Google scholar). Multicenter randomized controlled trial studies conducted in the English language were identified and screened. Joanna Briggs Institute quality assessment checklist for randomized controlled trials was used to critically appraise the methodological quality of studies. Analysis of individual studies was conducted using the OpenMeta-analyst and Review manager Version 5.3 software. The study was reported, according to the PRISMA reporting checklist.

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 (≤ 5 days) with a twice-a-day regimen (RR=1.138; 95% CI:1.008, 1.284) whereas on increased duration (>5days) azithromycin is almost similarly as effective as tobramycin with (RR=1.007; 95% CI: 0.964, 1.052). There was no significant difference in efficacy of bacterial resolution of azithromycin (1%, 1.5%) eye drops compared to tobramycin (0.3%) eye drops (RR=0.992; 95% CI: 0.967, 1.0183).

Conclusion: Azithromycin 1% and 1.5% eye drops are more effective in clinical cure rate than tobramycin 0.3% eye drops for short duration treatment. So that it is recommended to use azithromycin instead of tobramycin eye drops to get good result in short duration dosage.

Systematic Review Registration ID : CRD42019139911, registered on October 16, 2019;
Background
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 a number of gram-negative organisms. On the basis of 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 days course of other commonly used oral antimicrobials, administered two to four times a day, for the treatment of 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 percent of patients discontinuing therapy versus 2.6 percent 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 eradications 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 RCT studies proved that azithromycin ophthalmic solutions are effective for treatment of the above-mentioned eye diseases when compared with other antibiotics and a different
route. In spite of individual studies, there have been no conclusive investigations about the efficacy of ophthalmic solution in clinical cure rate and bacterial resolution. Therefore, the aim of this study was to abridge the conclusive evidence on the efficacy of azithromycin ophthalmic solutions for treatment of eye diseases compared to tobramycin eye drops and its effect on resolving clinical sign and symptoms of eye diseases.

Methods
Search strategy
The whole search was conducted by the investigators (BMA/lecturer and researcher/, TW/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 grey literature sources. 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 were searched. For unpublished studies and gray literatures 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 WHO trial registries were searched (See Additional file 1).

We do not have any regional or time restriction.

Study selection procedure
We included Randomized Controlled Trials and controlled clinical trials that have been conducted in all age groups and written in English language irrespective of duration/ time limitation. Studies with abstract only, not able to access the full article were excluded. Observational studies, reviews, commentaries, editorials, case series/report and patient stories were not included in the systematic review process. Articles extracted from different sources were exported to EndNote X8 citation manager, and duplicates were removed. The authors (BMA and TW) 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 through screening 26 studies were assessed for full. Finally, 11 studies were included in the final analysis (Fig. 1). The study was reported according to PRISMA reporting checklist (See 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 sign 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 (BMA and TW) independently using Joanna Briggs Institute (JBI) critical appraisal tool for Randomized Controlled Trials (9) (See 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 $\geq 50\%$ were included for the meta-analysis. Special focus was given to clear statement of the objective of the study, 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. Risk of bias in the included studies was assessed using the Cochrane Collaboration’s tool for assessing risk of bias in randomized trials (10) (Table 1). During critical appraisal and inclusion of the studies, the discrepancies arose between the authors were solved by consensus.
Table 1
Risk of bias of included studies

| Author, year | 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, 2007| Low                                        | Low                                    | Low                                 | Low                        | Low                                  | Low                              | Low                             |
| Bremond, 2014| Low                                        | Low                                    | Low                                 | Low                        | Low                                  | Low                              | Low                             |
| Cochereau, 2007| Low                                      | Low                                    | Low                                 | Low                        | Low                                  | Low                              | Low                             |
| Denis, 2008  | Low                                        | Low                                    | Low                                 | Low                        | Low                                  | Low                              | Low                             |
| Protzko, 2007| Low                                        | Low                                    | Unclear                             | Low                        | Low                                  | Low                              | Moderate                        |
| Robert, 2010 | Low                                        | Low                                    | Low                                 | Low                        | Low                                  | Low                              | Low                             |
| Bakar, 2009  | Low                                        | Unclear                                | Low                                 | Low                        | Low                                  | Low                              | Low                             |
| Haque, 2010  | Low                                        | Low                                    | Low                                 | Low                        | Low                                  | Low                              | Low                             |
| Luchs, 2008  | Low                                        | Low                                    | Low                                 | Low                        | Low                                  | Low                              | Low                             |
| Yildiz, 2018 | Low                                        | Low                                    | Low                                 | Low                        | Low                                  | Low                              | Low                             |
| Optiz 2011   | Low                                        | Low                                    | Low                                 | Low                        | Low                                  | Low                              | Low                             |

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 (BMA and TW) 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 (BMA and TW). Summary statistics (pooled effect sizes) in Relative Risk Ratios with 95% confidence intervals 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 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 Chi² test (Cochran’s Q-test) at p-value ≤ 0.05. The level of heterogeneity among the studies was quantified using the I² statistic described by Higgins et al (12) and P-value. A low P-value (less than 0.10) or a large I² statistic (I² >
75%) was considered as evidence of significant heterogeneity. Sensitivity analysis was employed to decrease the heterogeneity. A fixed-effect model was used. Publication bias were explored using visual inspection of the funnel plot. Besides, Egger’s regression was carried out to check symmetry of the funnel plot (11). 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 1509 articles through both electronic database and other sources. From the identified articles, 1019 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 were reviewed for eligibility and 15 of them were excluded due to inconsistent and incomplete outcome as well as differences in the study population. 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. A summary table of the included studies were also included (Fig. 1, Table 2 and Table 3).

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

| Study description of included studies | Study design/Outcome/ and participants | Sample size | Interventions | Key finding |
|---------------------------------------|----------------------------------------|-------------|---------------|-------------|
| Abelson, 2007/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 in DuraSite compared to tobramycin /Bacteriologically confirmed participants | Cure rate I = 159 C = 157 T = 316 Bacterial Resolution | IG: Participants received 1% azithromycin in DuraSite for 5 days CR: 127/159 CR: 123/157 BR: 140/159 BR: 148/157 |
| Bremond, 2014/France, Germany, Italy, Poland, Portugal, Romania, Algeria and Tunisia | To determine the efficacy and safety of azithromycin 1.5% eye drops in a paediatric population with purulent | Multicenter, international, RCT /Efficacy and safety of Azithromycin/children (from 1 day to 18 years old) | Cure rate I = 102 C = 101 T = 203 Bacterial resolution | IG: azithromycin 1.5% eye drops (one drop twice daily) CR: 48/102 CR: 29/101 Day 7 CR: 91/102 CR: 79/101 Day 7 BR: 85/102 |
| Study | Design | Participants | Methodology | Treatment Details | Outcome Measures | Key: | Reference |
|---|---|---|---|---|---|---|---|
| Cochereau, 2007/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 | Azithromycin 1.5% for 3 days compared to tobramycin for 7 days/ children and adults with purulent bacterial conjunctivitis. | Cure rate | IG: received either azithromycin 1.5% twice-daily for 3 days CG: tobramycin 0.3%, 1 drop every two hours for 2 days, then four times daily for 5 days | I = 245, C = 226, T = 471 | Day 3 CR: 203/226 Bacterial Resolution CR: 202/226 Bacterial Resolution |
| Denis, 2008/France, Bulgaria, Guinea Conakry, India, Morocco, Portugal, Romania, and Tunisia | To compare antibacterial efficacy of topically applied azithromycin 1.5% tobramycin 0.3% in a multicenter, randomized, investigator-masked study for the treatment of purulent bacterial conjunctivitis. | Multicenter, investigator-masked RCT | Bacterial resolution of topical therapy with azithromycin 1.5% for 7 days/ children, adult, infant and newborn patients at least 1 day of age and diagnosed with purulent bacterial conjunctivitis. | Bacterial Resolution | IG: azithromycin 1.5% eye drops (T1225, Théa Laboratories), one drop twice daily for 3 days CG: tobramycin 0.3% eye drops (Tobrex®, Alcon Laboratories), one drop every 2 hours while awake up to 8 times a day for 2 days, then one drop four times daily for 5 days. | I = 237, C = 216, T = 453 | Day 9 CR: 216/223 Bacterial Resolution CR: 215/245 Bacterial Resolution |
| Protzko, 2007/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 | Subjects with a clinical diagnosis of bacterial conjunctivitis at 47 sites | | IG: 1% azithromycin in DuraSite only twice a day on days 1 and 2 and daily on days 3 to 5 CG: 0.3% tobramycin | I = 159, C = 157, T = 316 | Day 5 CR: 147/159 Bacterial eradication rate CR: 147/157 Bacterial eradication rate |
| Robert, 2010/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 | Azithromycin 1.5% for 3 days compared to tobramycin for 7 days/ patients with purulent bacterial conjunctivitis. | Cure rate | IG: azithromycin 1.5% twice daily for 3 days CG: Patients received tobramycin 0.3%, 1 drop every 2 hours for 2 days, then four times daily for 5 days | I = 245, C = 226, T = 471 | Day 9 CR: 216/246 Bacterial Resolution CR: 203/227 Bacterial Resolution |

Key: | I- intervention; C- control; IG- Intervention Group; CG- Control Group; CR- Cure Rate; BR- Bacterial Resolution
Cure rate of azithromycin (1% and 1.5%) compared to tobramycin (0.3%) eye drops

Five multicenter RCTs was 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 of the included studies used 1% and 1.5% azithromycin as the intervention compared with 0.3% tobramycin in the control arms. Two out of five studies reported the clinical cure rate of azithromycin ophthalmic solutions is more effective than tobramycin eye drop (5, 6). In another way, the rest three studies were reported that there was no significant difference in efficacy (13, 14, 6). This meta-analysis was based on 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 = 1.138; 95% CI: 1.008, 1.284). Whereas on increased duration (> 5 days), azithromycin is as effective as tobramycin with (RR = 1.007; 95% CI: 0.964, 1.052) (Fig. 2).

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

Five out of six RCTs reported bacterial resolution rate of azithromycin compared to tobramycin eye drops (5, 6, 13, 15, 16). The overall finding of these studies showed that there is no statistically significant difference in bacterial resolution between azithromycin and tobramycin eye drops (RR =

| Author, year | Eye symptom scores Before Mean ± SD (median) | Eyelid finding scores Before Mean ± SD (median) | Conjunctival hyperemia Before Mean ± SD (median) | Schirmer test (mm) Before Mean ± SD (median) | Meibomian Gland secretion Before Mean ± SD (median) | TBUT (sc) Before Mean ± SD (median) | Ocular surface staining scores Before Mean ± SD (median) | Cure rate of azithromycin (1% and 1.5%) compared to tobramycin (0.3%) eye drops |
|--------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Bakar, 2009  | 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)                              | 7.78±3.52 (8.00)                              |
| Haque, 2010  | 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)                              | 1.36±0.66 (1.00)                              |
| Luchs, 2008  | 3.2±0.65 (0.64)                               | 1.1±0.64 (0.77)                               | 1.97±0.61 (0.67)                              | 0.67±0.61 (0.67)                              | 1.80±0.56 (0.67)                              | 0.47±0.56 (0.67)                              | 17.73±3.56 (20.46)                             | 7.87±1.51 (8.39)                              |
| Yildiz, 2018 | 2.33±0.49 (0.65)                              | 0.62±0.65 (0.56)                              | 2.20±0.56 (0.61)                              | 0.61±0.56 (0.61)                              | 1.80±0.56 (0.61)                              | 0.47±0.56 (0.61)                              | 20.46±1.98 (21.3)                             | 8.39±1.26 (8.39)                              |
| Optiz, 2011  | 2.73±0.89 (2.21)                              | 0.78±0.78 (2.21)                              | 2.21±0.74 (2.1)                               | 1.54±0.73 (2.21)                              | 1.43±0.65 (2.1)                               | 1.62±0.57 (2.1)                               | 24.4±1.67 (24.4±1.67)                         | 1.00±0.51 (1.00)                              |
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 = 0.992; 95% CI: 0.956, 1.030) and long (> 5 days) (RR = 0.992; 95% CI: 0.958, 1.027) duration treatments, the bacterial resolution rate of azithromycin eye drops is similar with that of tobramycin (Fig. 3).

Efficacy of Azithromycin Ophthalmic Solutions (1%, and 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, 17–19) 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 the 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 (RR=-1.42; 95% CI: -1.76, -1.09). The finding revealed there was significant statistical heterogeneity (I^2 = 82%, \( \chi^2 = 22, P = 0.0002 \)) (Fig. 4).

Eyelid finding scores

Four of the studies (7, 8, 17, 19) reported the clinical efficacy of Azithromycin ophthalmic solutions in improving eyelid finding scores. The standardized mean difference of these studies indicates that there is statistically significant improvement in the severity of eyelid finding scores (RR = -1.94; 95% CI: -2.36, -1.52) (Fig. 5).

Meibomian Gland secretion

Blepharitis, meibomian gland dysfunction and other ocular diseases lead to dry eye due to decreased secretions (20–22). Three RCTs (17, 18, 19) was found to report the effect of azithromycin in improving meibomian gland secretion. The pooled estimate of the studies revealed that patients treated with Azithromycin showed statistically significant improvement in meibomian glad secretion (RR = -1.78; 95% CI: -2.25, -1.30) (Fig. 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 (7,8,18,19) 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 disease with (RR = -0.57; 95% CI: -0.88, -0.25) (Fig. 7).

**Tear break up 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 seconds is considered abnormal (24). The overall effect of Azithromycin treatment from four RCTs showed that TBUT is significantly improved with (RR = 0.31; 95% CI: 0.00, 0.62) (Fig. 8).

**Schirmer test in mm**

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 increase in the Schirmer test value after study subjects are treated with azithromycin eye drops. The pooled estimate of these studies is in consistent with individual studies (RR = 0.54; 95% CI: 0.17, 0.91) (Fig. 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 (7, 8, 19) reported the effect of Azithromycin eye drops for conjunctival hyperemia due to different eye diseases. The pooled estimate of these studies indicates azithromycin ophthalmic solutions were effective in decreasing conjunctival hyperemia with (RR = -1.09; 95% CI: -1.49, -0.69) (Fig. 10).

**Discussion**

This systemic review and meta-analysis presented the abridge evidence on the efficacy of azithromycin ophthalmic solutions for treatment of eye diseases compared to tobramycin eye drops and its effect on resolving clinical sign and symptoms of eye diseases by summarizing primary RCTs. A total of 11 studies that have been critically appraised using Joanna Briggs Institute (JBI) assessment
checklist, undertaken in different countries in the world, were identified and included. Even though we identified included similar studies, the duration of the drug and its efficacy were different, we performed subgroup analysis. The studies conducted in non-English language and studies with incomplete abstract were excluded because of inaccessibility of the complete data.

This study clearly infers that azithromycin ophthalmic solution is a better treatment choice than tobramycin eye drops to rapidly eradicate bacteria, mainly in less than or equal to five days treatment for two 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 (47.1% vs 28.7%) (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 (15). However, it is contradicted by a randomized trial study, which was reported that bacterial eradication was 88.1% in the 1% azithromycin in DuraSite group vs 94.3% in the tobramycin group (95% CI: −12.4–0.0) (5). Despite this, most of the studies were on the support of the efficacy of the azithromycin eye drop in eradication of bacteria in short day 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 (7, 8, 17); eyelid finding scores; meibomian gland secretion (17, 18, 19), ocular surface staining scores (7, 18,19), tear breakup time in seconds (7, 8,18, 19), Schirmer test in mm (8,18,19) and conjunctival hyperemia (7, 8, 19) with less than five days azithromycin ophthalmic solutions treatment.

**Conclusion**
Azithromycin 1% and 1.5% eye drops are more effective in eradicating most pathogenic bacteria associated with eye disease than tobramycin 0.3% eye drops for short duration treatment. It is also the best choice of treatment for the improving the signs and symptoms of the eye disease. It has also convenient dosage form. So that it is recommended to use azithromycin instead of tobramycin eye drops to get good result in short duration.

**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 were not included studies conducted other than the English language and studies with incomplete information. Additionally, the heterogeneity of the study, which was due to variation between studies in characteristic of the study population, medical and nonmedical factors as a reason for the variation between studies.

Abbreviations

RCT
Randomized Controlled Trials
JBI
Joanna Briggs Institute
RR
Risk Ratio
CI
Confidence Interval
TBUT
Tear Breakup Time

Declarations

Ethics approval and consent to participate
Not Applicable

Consent for publication
Not Applicable

Availability of data and material

The datasets analysed during the current study are available in the Table 2 and Table 3. Selected search strings and strategies, Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement 2009 Checklist and Critical appraisal for a Randomized Controlled Trials Study are attached as additional files 1, 2 and 3 respectively.

Acknowledgments
We would like to address our deepest gratitude to the authors of the included studies for this systematic review and meta-analysis. Our deepest gratitude also goes to the staffs of Haramaya University, College of Health and Medical Sciences who gave us technical support.

Authors' Contributions
BMA*, TW, conceived and designed the review. BMA* and TW carried out the draft of the manuscript and BMA* is the guarantor of the review. BMA* and TW developed the search strings. BMA* and TW screened and select studies. BMA* and TW carried out analysis and interpretation. BMA* and TW rigorously review the manuscript. Both authors read and approved the final version of the manuscript.

Competing Interests: The authors declare that they have no competing interests.

Funding: The authors did not receive any funding from any funding agency or organization.

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Figures
Figure 1

PRISMA flow chart showing study selection process
Clinical cure rate of azithromycin ophthalmic solutions compared to tobramycin eye drop

Bacterial resolution rate of azithromycin ophthalmic solutions compared to tobramycin eye drop.
Effect of azithromycin eye drops (1%, 1.5%) on eye symptom scores

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

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

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 mm
| Study or Subgroup | Mean | SD  | Total | Mean | SD  | Total | Weight | IV, Fixed, 95% CI | Std. Mean Difference | IV, Fixed, 95% CI |
|-------------------|------|-----|-------|------|-----|-------|--------|-------------------|----------------------|-------------------|
| Bakar 2009        | 0.94 | 0.72| 18    | 1.39 | 0.6 | 18    | 36.1%  | -0.66 [-1.34, 0.01] |                      |                   |
| Haque 2010        | 1.3  | 0.56| 23    | 1.8  | 0.5 | 26    | 46.5%  | -0.93 [-1.52, -0.34] |                      |                   |
| Yildiz 2018       | 0.47 | 0.52| 15    | 1.8  | 0.56| 15    | 17.5%  | -2.39 [-3.36, -1.43] |                      |                   |
| Total [95% CI]    |      |     | 56    |      |     | 59    | 100.0% | -1.09 [-1.48, -0.69] |                      |                   |

Heterogeneity: $\chi^2 = 8.91, df = 2 (P = 0.01); I^2 = 77\%$

Test for overall effect: $Z = 5.29 (P < 0.00001)$

**Figure 10**

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

**Supplementary Files**

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