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RESEARCH ARTICLE **OPEN ACCESS**

THE EFFECT OF LEVOFLOXACIN ADDITION ON THE OUTCOME OF TUBERCULOUS MENINGITIS PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: Tuberculous meningitis (TBM) is one of tuberculosis's deadliest extra-pulmonary manifestations. Although early initiation of anti-tuberculosis drugs can reduce mortality and morbidity, poor blood-brain barrier penetration hampered their effectiveness. Levofloxacin is an anti-tuberculosis drug with good BBB penetration.
Objective: We aim to explore whether levofloxacin addition to the TBM patients' regimen has a potential benefit to improve their outcomes.
Methods: The literature search was done on PubMed, Google Scholar, and ProQuest databases without publication date limits to identify studies investigating the effect of augmenting levofloxacin in the outcome of TBM patients. The primary outcome of this study was to analyze the impact of these regimens in decreasing the risk of death and neurological deficit. The articles were collected using the PRISMA diagram, critically appraised using PICO analysis, then the data were analyzed using Review Manager 5.4.1 software with a Fixed Effect Model. The results were expressed as odds ratio (OR).
Results: Four randomized controlled trials with a total of 930 patients were identified. Two trials compared the effectiveness of levofloxacin addition only, whereas the other two used the regimen containing the increased dose of rifampicin alongside levofloxacin addition. Based on the analysis, neither levofloxacin addition only nor increasing rifampicin dose with levofloxacin addition had a significant impact on the mortality of TBM patients (OR=0.55; 95% CI 0.19-1.59; p=0.27, OR=1.01; 95% CI 0.74-1.36; p=0.97, respectively).
Conclusion: Additional Levofloxacin on TBM treatment shows no significant improvement in patient mortality. Routine levofloxacin use in TBM is discouraged due to limited evidence.

Keywords: levofloxacin, rifampicin dose, treatment, tuberculous meningitis

Introduction

Tuberculous meningitis (TBM) is an extra-pulmonary manifestation of tuberculosis (TB) in the central nervous system which is often misdiagnosed due to its similarity with other meningitis.[1] The global burden of this disease remains unclear; however, it is estimated that about 100.000 people develop TBM annually.[2] Immunosuppressed people and children are predominantly affected. In the absence of TB treatment, the outcomes are very poor, with a 30% mortality rate and half of them suffer from neurological deficits.[3,4]

Although early initiation of anti-tuberculosis drugs can reduce mortality and morbidity, poor blood-brain barrier (BBB) penetration hampered their effectiveness.[3,5,6] For instance, either streptomycin or ethambutol exhibits poor cerebrospinal fluid (CSF) penetration, while the standard dose of rifampicin may not reach the minimum inhibitory concentration for TB in CSF.[7] Levofloxacin is an anti-tuberculosis drug with good BBB penetration and has been used for multi-drug resistant TB. (5,8–10) Therefore, levofloxacin addition to the TBM patients' regimen has a potential benefit to improve their outcomes.

Methods

1. **Search and Study Selection**

   This is a systematic review and meta-analysis. The literature search was done through PubMed, Google Scholar, and ProQuest databases without publication date limits to identify studies investigating the effect of augmenting levofloxacin in the outcome of TBM patients with this keyword ("Tuberculous Meningitis" OR "TB Meningitis" OR TBM) AND (Levofloxacin OR LFX).

   The process of study selection encompassed two stages. Initially, two reviewers screened titles and abstracts. Subsequently, in cases where abstracts lacked clarity, the full-text articles of selected studies were obtained and reviewed. Data extraction was performed using an Excel spreadsheet, encompassing details such as author, publication year, participant characteristics, HIV status, anti-tuberculosis regimens used, and the recorded outcomes.

2. **Type of Intervention**

   The interventions described in the selected articles include either the addition of levofloxacin to the standard first-line regimen (HRZE/S) or the use of levofloxacin in conjunction with an intensified regimen (comprising high-dose rifampicin along with HZE/S). In contrast, the control arm received standard anti-tuberculosis treatment that did not incorporate levofloxacin. The primary outcome of this study is mortality rate, whereas the secondary outcome is neurological disability at the end of follow-up.

3. **Data Extraction and Analysis**

   The articles were collected using the PRISMA diagram and critically appraised using PICO analysis (Figure 1). The risk of bias for each study was assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (Table 2).[11] The data were analyzed using Review Manager 5.4.1 software with a Fixed Effect Model. The results were expressed as odds ratio (OR). We assessed heterogeneity by visually inspecting the forest plots as well as by using an I^2 statistics, with an I^2 value of ≥ 50% interpreted as statistical heterogeneity.

Results

The initial search yielded 548 articles. After removing duplicates, irrelevant articles, literature reviews, systematic reviews, and meta-analyses, we identified nine randomized controlled trials (RCTs) investigating levofloxacin interventions in TBM patients. Among these, three RCTs were excluded as they constituted sub-studies of other RCTs involving the same set of patients. Additionally, one RCT was excluded due to its status as a study protocol, while another was omitted because the intervention arm employed levofloxacin as a replacement for rifampicin.

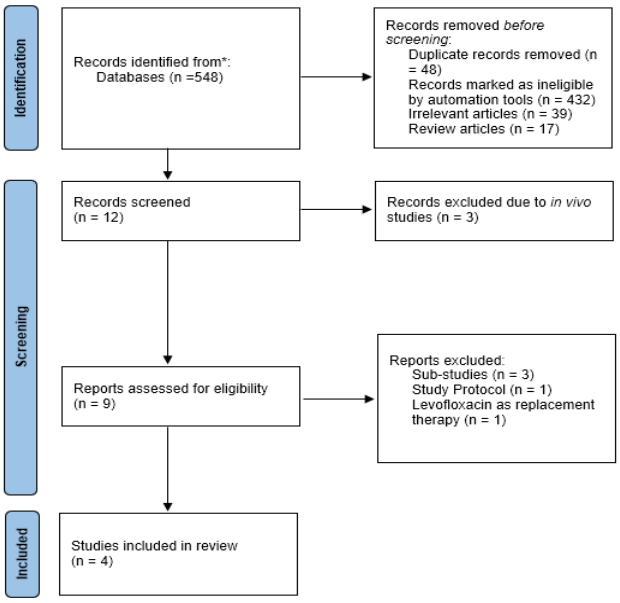


Figure 1. PRISMA Diagram

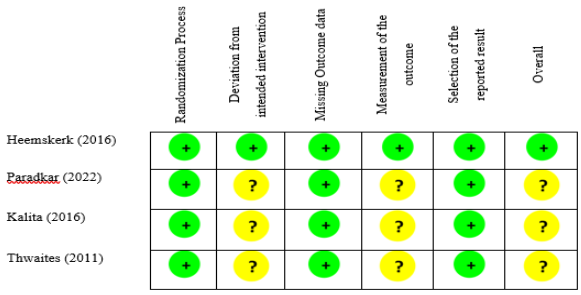
Four randomized controlled trials with a total of 930 patients were identified. Two trials compared the effectiveness of levofloxacin addition only,[5,10] whereas the other two used the regimen containing the increased dose of rifampicin alongside levofloxacin addition.[8,9] Characteristics of the included studies are depicted in the table below (Table 1).

Table 1. Characteristics of the included studies

Author (Year)	Country	Age	Intervention Arm	Follow-Up
Heemskerk (2016)	Vietnam	≥ 18 (29-47) years	LFX+High Dose R+HZE	9 months
Paradkar (2022)	India, Malawi	6 months-12 years	LFX+High Dose R+HZE	52 weeks
Kalita (2016)	India	15-75 years	LFX+RHZE	6 months
Thwaites (2011)	Vietnam	≥ 14 (15-82) years	LFX+RHZE	270 days

All included trials reported adequate randomization methods using computer-generated allocation. Therefore, they were classified as having a low risk of selection bias. Additionally, the trials exhibited a loss to follow-up of less than 10%, further contributing to their classification as having a low risk of attrition bias. Blinding and a pre-specified protocol were only available in the study conducted by Heemskerk *et al.*, rendering the potential for unclear selection and performance bias in the remaining studies. Nevertheless, given that all included studies reported the outcomes as outlined in the methods, the risk of reporting bias is low.

Table 2. Risk of Bias



Based on the analysis, neither levofloxacin addition only nor increasing rifampicin dose with levofloxacin addition had a significant impact on the mortality of TBM patients (OR=0.55; 95% CI 0.19-1.59; p=0.27, OR=1.01; 95% CI 0.74-1.36; p=0.97, respectively) (Figure 2 and Figure 3).

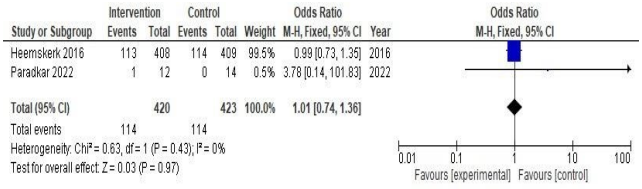


Figure 2. Forrest Plot of Intensified Rifampicin + Levofloxacin in TBM Patients

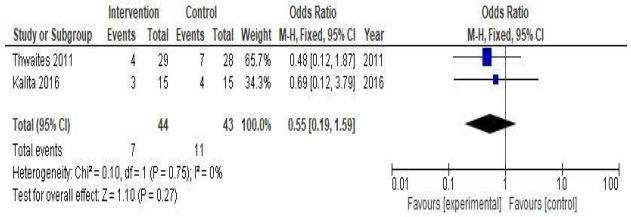


Figure 3. Forrest Plot of Levofloxacin Addition Only in TBM Patients

Because the only articles that supplied data on neurological disability were those by Paradkar et al (2023) and Kalita et al (2016), we were unable to perform a statistical analysis on this particular outcome owing to variations in the treatment protocols. Nonetheless, the TBM-KIDS trial demonstrated swift improvement across all groups, with no participants exhibiting neurological disabilities by week 24.[9] In contrast, Kalita et al (2016) documented that among the subjects, 5 out of 25 experienced neurological disabilities in the fluoroquinolone group, while the standard regimen group had 3 out of 21 subjects (14.28%) affected.[5]

Discussion

This systematic review aimed to assess the impact of incorporating levofloxacin into the drug regimen of TBM patients. Notably, two trials adopted a combination of an elevated rifampicin dosage and levofloxacin supplementation, driven by concerns that the prevailing rifampicin dose might not achieve the minimum inhibitory concentration (MIC) in cerebrospinal fluid (CSF) to effectively eliminate tuberculosis.[12]

The inclusion of two trials utilizing the combined regimen revealed a significant degree of heterogeneity (I2=0.63). It might happen due to the different populations of the two studies. Heemskerk et al. (2016) conducted a trial involving adults, while Paradkar et al. (2022) focused on the pediatric population.[8,9] Moreover, due to the COVID-19 pandemic and slow enrollment pace, Paradkar et al. (2022) could not achieve the targeted sample size. Consequently, the study was limited by a relatively small number of subjects available for analysis. Our analysis showed that this combined regimen did not reduce the mortality of TBM patients (OR=0.55; 95% CI 0.19-1.59; p=0.27).

The other two RCTs incorporated levofloxacin only as part of their intervention strategy. Although the number of deaths is fewer in the intervention arm, this difference was not statistically significant (OR=1.01; 95% CI 0.74-1.36; p=0.97).

In line with the World Health Organization's (WHO) recommendations, the application of fluoroquinolones, including levofloxacin, is endorsed for the treatment of multidrug-resistant tuberculosis (MDR-TB).[13] However, the scarcity of data concerning drug-resistant tuberculous meningitis necessitates the management of such patients based on pulmonary tuberculosis guidelines. Furthermore, the WHO underscores the use of second-line drugs with robust cerebrospinal fluid penetration for managing these challenging cases.[13,14]

While this systematic review does not advocate for the routine utilization of levofloxacin in TBM patients, especially in light of the analyzed data, it acknowledges the continued relevance of its usage in specific scenarios such as drug-resistant TBM.

Conclusion

Additional Levofloxacin on TBM treatment shows no significant improvement on patient's mortality. Routine levofloxacin use in TBM is discouraged due to limited evidence. It is strongly recommended to explore the potential of Levofloxacin in special cases such as drug-resistant TBM.

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