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USE OF HIGH DOSE RIFAMPICIN FOR THE TREATMENT OF TUBERCULOSIS MENINGITIS PATIENTS: A SYSTEMATIC REVIEW

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Abstract

Background:

Aim: *The objective of this study is to summarize and evaluate the use of high-dose rifampicin for the treatment of tuberculosis meningitis.*

Methods: *A systematic search strategy was conducted across several electronic reference databases (PubMed, Cochrane Library, Google Scholar) and included articles published between 2018–2023. Duplicate publications, review articles, and incomplete articles were excluded.*

Results: *Database searches identified a total of 93 articles. Of these, 22 articles passed the screening process and resulted in 12 articles for full-text assessment. The 6 articles did not evaluate the outcome of interest. Hence, we found 6 appropriate studies included in this review.*

Conclusion: *The results suggest that high-dose rifampicin is not associated with the outcomes of tuberculosis meningitis patients. However, further research especially RCTs is recommended to evaluate comprehensive rifampicin regimens for the optimization of tuberculosis meningitis patients.*

Keywords: *High-dose rifampicin, treatment, tuberculosis meningitis*

INTRODUCTION

As the leading cause of mortality and morbidity in the world, Tuberculosis (TB) has approximately 1.4 million deaths in 2019. The World Health Organization (WHO) also reported around 8 million TB cases annually. Extrapulmonary tuberculosis constitutes 6.05% of cases of tuberculosis in Indonesia[1,2]. TB has become the most common infectious disease in recent years owing to the increase of *Mycobacterium tuberculosis* (*M. tuberculosis*) multidrug resistance and intolerance to treatment[3]. The incidence is highest in TB meningitis (TBM). In addition, TB meningitis has severe clinical manifestations such as stroke, vomiting, confusion, and decreased mental condition that could result in neurological complications or morbidity if not treated properly[4,5].

The sign and symptoms of tuberculosis meningitis emerged due to the tuberculosis bacillus' rapid dissemination that advanced into the focal neurological defect[6,7]. Poor prognosis is indicated if there is damage in the basal ganglia. Despite the morbidity, tuberculosis meningitis has its' own challenges in the diagnosis due to the similarity of manifestations with other neurological diseases[8,9]. As the deadliest form of TB, complications of tuberculosis meningitis are life-threatening cerebral vasculitis and hydrocephalus. The evidence related to the management of tuberculosis meningitis is essential to increase survivability, minimize morbidity and resolve the complications of tuberculosis meningitis[10,11].

Currently, WHO suggested the treatment of tuberculosis meningitis with rifampicin (RMP), isoniazid (INH), pyrazinamide (PZE), and ethambutol (ETB) for 2 months and followed with RMP and INH for all patients for the duration of 10 months. The earlier the patient is initiated with the regimen, the higher the survivability[11]. However, the dose of rifampicin to achieve maximum tuberculosis meningitis treatment is a concern. Several studies recommended low doses while others recommended higher-dose. An example of the research is an open-label randomized phase II study in 2013 that showed a 50% mortality reduction with a rifampicin dose of 450 mg or 10 mg/kg, as opposed to the study in Vietnam between 2011 and 2014 that showed different results with an oral dose rifampicin of 15 mg/kg. Albeit the results, the use of rifampicin is still scarce in Indonesia[2,6,7,12]. Therefore, this review is intended to give new insights into the use of high-dose rifampicin in the treatment of tuberculosis meningitis to decrease mortality and morbidity and as the basis of treatment also future research in the field of study.

Method

Search Strategy

This study is a qualitative systematic review. The data is obtained through electronic database search in Medline (PubMed), Cochrane Library, and Google Scholar. The keywords are "High-dose rifampicin" AND "Tuberculosis meningitis" using English and Bahasa Indonesia. The selected articles are based on inclusion and exclusion criteria.

Table 1. Literature search strategy

Database	Keywords	Results
PubMed	"High-dose rifampicin" AND "Tuberculosis meningitis"	13
Cochrane Library	"High-dose rifampicin" AND "Tuberculosis meningitis"	20
Google Scholar	"High-dose rifampicin" AND "Tuberculosis meningitis"	60

Eligibility Criteria

All studies were assessed for eligibility. The inclusion criteria of the included studies were articles published in the last 5 years between 2018 and 2023, full-text articles, published in Bahasa Indonesia or English, and studied the use of high-dose rifampicin in the treatment of tuberculosis meningitis. This review also selected the articles based on population which are patients clinically and bacteriologically diagnosed with tuberculosis meningitis, intervention which is high-dose rifampicin that is more than 10 mg/kg in adult and 15 mg/kg in pediatric, comparison which is the standard rifampicin dose 10 mg/kg, lastly, outcomes which are safety and efficacy. The exclusion criteria of the studies are articles that are not indexed by Scopus, editorials, reviews, and articles that did not report complete data on the dosage of rifampicin, the subjects, the results, or the adverse events. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline is used for the selection. Finally, the articles are screened and synthesized into a qualitative systematic review.

Data Extraction and Outcome

All the authors extracted the data from the articles. Author, year of study, published year, study design, treatment, outcome, and complication of the patients in the study were identified for qualitative analysis.

Results

Databases search identified a total of 93 articles (Table 1). Of these, 22 articles passed the screening process and resulted in 12 articles for full-text assessment. Among them, 6 articles did not evaluate the outcome of interest. Hence,

we found 6 appropriate studies included in this review (Figure 1). The summary of the main findings of the selected studies is presented in Table 1. The selected studies included a total of 441 subjects.

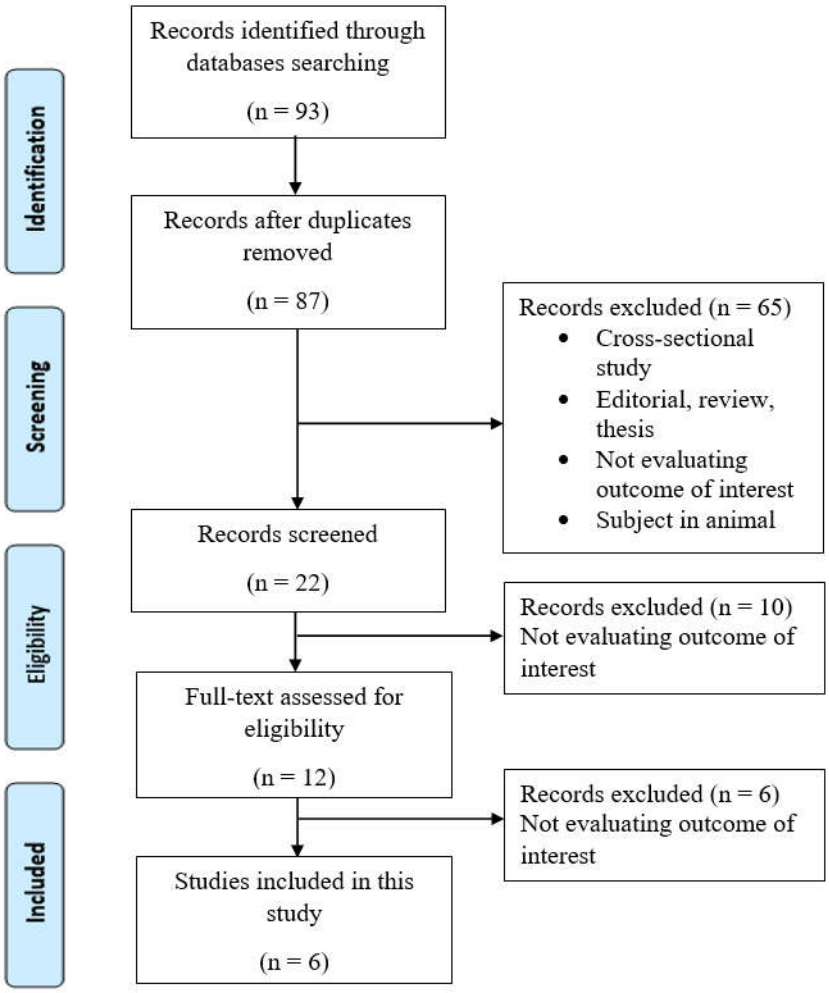
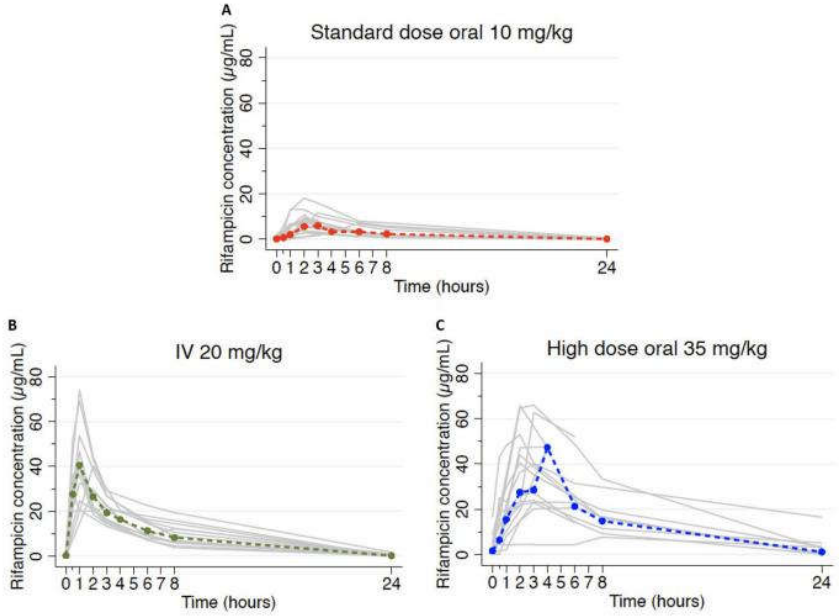


Figure 1. PRISMA flow diagram

Table 1. Summary of included studies

Author (Year)	Study design	Country	N	Dosage	Duration	Age (Years)	Follow-up	Findings
Dian et al. (2018)[13]	Double-blind RCT	Indonesia	60	- Double dose (20 mg/kg) - Triple dose (30 mg/kg)	30 days	29.5	6 months	- Double and triple-dose oral rifampicin have 3- and 5-fold higher geometric mean total exposures in plasma in the critical early days without an increase in grade 3 or 4 adverse events - The mortality is lower (15%) compared to standard dose group (35%) and tripling in rifampicin is considered safe.
Ding et al. (2020)[14]	Double-blind RCT	Vietnam	237	15 mg/kg	2 months	>14	9 months	No relationship between rifampicin dose and survival
Wasserman et al. (2021)[15]	RCT	South Africa	46	- 20mg/kg intravenous - 35 mg/kg oral dose	5 days	30-45	6 months	The plasma rifampicin geometric mean area under the concentration-time curve from 0 to 24 hours was higher in 35 mg/kg dose orally than intravenous administration
Paradkar et al. (2022)[16]	Open-label RCT	India and Malawi	37	30 mg/kg	2 months	70.2 ± 9.6	6 months-12 years	Better neurocognitive outcomes in pediatric
Cresswell et al. (2021)[17]	Open-label RCT	Uganda	61	- 20mg/kg intravenous - 35 mg/kg oral dose	2 months	≥18	6 months then referred to local TB services	- High-dose intravenous and oral rifampicin were safe - Exposures 6- and 8-fold higher than standard dose - Cerebrospinal fluid (CSF) levels above the minimal inhibitory concentration (MIC) ($p<0.001$)
Garcia-Prats et al. (2021)[18]	Prospective cohort	South Africa	14	- 35 mg/kg - 50 mg/kg - 60 mg/kg - 75 mg/kg	2 weeks	0-12	2 weeks	- All dosage were safe to be given - 65-70 mg/kg dosage are required to approximate target exposures in pediatric

This review identified several characteristics in the use of high-dose rifampicin for the treatment of tuberculosis meningitis. The included articles were randomized clinical trials (RCTs) from six countries (Indonesia, Vietnam, South Africa, India, Malawi, and Uganda). The studies compared the use of high-dose rifampicin in the dosage of more than 10 mg/kg. Among them, all studies evaluated oral rifampicin at 15, 20, and 35 mg/kg and intravenous rifampicin at 20 mg/kg. The duration of given treatment is 5 days shortest and 2 months longest, with more than 6 months follow-up. The studies evaluated the efficacy and adverse effect of Rifampicin such as mortality and side effects[13–18].



Picture 1. Individual concentration-time profiles for oral and intravenous high-dose Rifampicin compared to standard dose oral.

In the studies, high dose of rifampicin was not associated with adverse events, mainly grade 3 and 4. In a study by Paradkar et al. (2022), high-dose rifampicin was considered to have better pediatric neurocognitive outcomes indicated by Modified Rankin Scale (MRS)[16]. Similar results were seen in adult population in a clinical trial by Cresswell et al. (2021)[17]. The found adverse events in the study by Garcia-Prats et al. (2021) were below grade 3 therefore the use of high-dose rifampicin for tuberculosis meningitis considered safe in children and adults[18].

Ding et al. (2020) found that 15 mg/kg dose of Rifampicin increased exposures in CSF and plasma if compared with standard 10 mg/kg dose. Albeit the elevated number, there was no relationship between rifampicin exposure and the survival of the patients[14]. Wasserman et al. (2021) investigated the use of oral and intravenous rifampicin dose. After 35 mg/kg dose was given, the plasma rifampicin geometric mean area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) was higher in oral group with respect to intravenous dosage[15]. The efficacy was also higher in the oral group. In the cohort study by Garcia-Prats et al. (2021), the dosage of 65-70 mg/kg was tolerable without serious adverse effects and required to achieve target exposures equal to adults that are receiving 35 mg/kg. The dosage was safe to be given to 14 days[18].

Discussion

In this review, we found that the use of high-dose rifampicin in the treatment of tuberculosis meningitis is safe with tolerability both in pediatric and adult population[10,19]. The optimal dose to reach target exposures were 65-70 mg/kg and 35 mg/kg respectively for each group, due to higher need of bioavailability in pediatric population. In addition, children who are less than 3 years of age are having reduced absorption of rifampicin[18]. If compared to adults, children have lower gastric pH, thus minimized absorption[20,21]. A higher dose of rifampicin resulted in a pharmacokinetic target attainment increase with an explanation of increase in AUC_{0-24} compared with standard dose. Despite the promising studies, there is also a study that revealed similar efficacy between low- and high-dose rifampicin[14]. To specifically evaluate the efficacy of high-dose rifampicin, further clinical trial is needed. The use of oral high-dose rifampicin is more effective since widely available in low-to-middle-income countries due to cheaper costs and feasible after hospital discharge[12,15,22,23].

The most common adverse effect was vomitting. This may be due to the gastrointestinal effects in cause of the large pill burden, high dosages, and formulation, which more to be found in pediatric population[16]. A study in Indonesia revealed that higher rifampicin plasma exposure, compared with standard treatment, was associated with lower mortality. The research also align with a 35 mg/kg dose of rifampicin in Africa with higher bactericidal properties in high-dose group rifampicin[23–25]. High-dose rifampicin may be beneficial in improving tuberculosis meningitis outcomes without significant morbidity and mortality[5,20,21,26]. In addition of the treatment, it is also important to address the onset of diagnosis and treatment. We found in the included articles that majority of the patients were in tuberculosis meningitis Grade II[16,17].

There are several limitations in this systematic review. First, all of the included articles were performed in developing countries, hence lower applicability in developed countries. However, the incidence of meningitis tuberculosis is higher in developing countries. Second, there are variations in treatment periods. We recommend a further large-scale study of RCTs to confirm the applicability of high-dose rifampicin mainly in Indonesia.

Conclusion

This systematic review demonstrated that high-dose rifampicin for tuberculosis meningitis treatment is considered safe with the dosage of 35 mg/kg for adults and 65-70 mg/kg for pediatric population in order to achieve proper bioavailability and target exposure. The duration of rifampicin can be given for two months. High-dose rifampicin is associated with better efficacy and bactericidal properties. A further large-scale clinical trial is recommended to evaluate specific dose in the incidence of adverse events.

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