ORIGINAL RESEARCH

Study of use of rifampicin plus levoflixacin for the treatment of tuberculosis meningitis in children

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ABSTRACT

Background: Pediatric tuberculous meningitis (TBM) in children frequently results in death or permanent impairment. High-dose rifampicin may lower mortality in adults, however role of fluoroquinolones in combination with rifampicin is yet unknown. **Objective:** To evaluate the effect of combination of effects of levofloxacin and rifampicin in the management of TBM in children and compare the efficacy against standard of care. **Methods:** Pediatric patients with TBM were enrolled for the study after parental interviews and clinical assessment. Children were randomized to receive high-dose rifampicin and ethambutol (R30HZE, Arm 1), high-dose rifampicin and levofloxacin (R30HZL, Arm 2) or standard-of-care treatment according to the World Health Organization recommendations (HR15ZE, Arm 3). Modified Rankin Scale (MRS) and other neurological test were performed to assess the efficacy of treatment along with safety profile. **Results:** 25 children were enrolled for the study with a median age of 7.2 years. Stage I, II, and III illness was present in 24%, 32%, and 24% of cases, respectively and of them, 13 (52%) had definite TBM. In arms 1-3, the median (range) MRS scores at admission were 3 (1–4), 2 (1–4), and 2 (1–5), respectively. By week 8, all arms had shown rapid progress, and by week 24, nearly all of the kids had recovered to a score of 0 or 1, which indicates little to no handicap. After correcting for age and baseline MRS, children receiving high-dose rifampicin (arm 1) in neurocognitive tests showed statistically significant improvements in their longitudinal scores for fine motor, receptive language, and expressive language when compared to SOC. **Conclusion:** The functional results of a pediatric TBM study were quite good. It will need a bigger trial to validate the pattern that child receiving high-dose rifampicin had better neurocognitive results but a higher number of adverse events.

Keywords: Pediatric tuberculous meningitis, Neuropsychological assessment, Clinical efficacy, High-dose rifampicin, Levofloxacin

INTRODUCTION

One of the biggest issues with world health is tuberculosis (TB). Tuberculous meningitis (TBM) is the most severe disease produced by Mycobacterium tuberculosis (Mtb) of all other illnesses [1]. The death rate for tuberculosis has decreased since the 1950s when streptomycin was first used as an antibiotic [2]. Nonetheless, overall rates of morbidity and death remain high. When MTB bacilli are injected into the meninges, extrapulmonary tuberculosis is shown [2]. The alveolar macrophage gets infected with MTB by droplet inhalation, which is the initial method of infection. The lung is the site of the original infection, which spreads to the lymph nodes. A high level of bacteremia can spread throughout the entire body at this stage of the infectious process [3]. MTB seeds the meninges in tuberculous meningitis, thereafter they form sub-ependymal collections known as Rich foci. These foci have the potential to burst into the subarachnoid space, which would trigger a severe inflammatory reaction and symptoms similar to meningitis [4]. Nerve palsies may result from the exudates produced by this reaction encasing cranial nerves [4]. They can obstruct the passage of cerebral spinal fluid (CSF), which can result in hydrocephalus, and ensnare blood vessels, which can cause vasculitis [5]. It is estimated that about one-third of people on the planet are MTB positive [6]. Despite improvements in therapy and global initiatives to make drugs and standardised treatment programmes accessible to all, the number of people infected with TB remains high.

It is challenging to predict which TB-infected patients may get tuberculous meningitis. Children are more likely to get MTB in underdeveloped nations, where this virus is more common. TBM is more common in children with MTB, particularly in those between the ages of 0 and 4 [7]. TBM is one kind of disseminated tuberculosis (TB) that young children are particularly vulnerable to [8,9]. Even though neurologic injury can happen to patients of any age due to direct bacterial effects, host-response vasculitis, or blockage of the cerebrospinal circulation [10], children are particularly at risk for developmental sequelae because the disease and its treatment coincide with crucial stages of neurocognitive development [11].

The treatment of TBM is not well supported by data, especially when it comes to anti-tubercular chemotherapeutic regimens. Worldwide treatment regimens for TBM vary and are primarily derived from those for pulmonary tuberculosis. As for pulmonary TB, the World Health Organization (WHO) currently recommends the same standard of care (SOC) for treating TBM: an intensive phase of isoniazid, rifampicin, pyrazinamide, and ethambutol lasting two months, followed by a continuation phase of isoniazid and rifampicin at the same doses as for pulmonary TB [12]. The extension of TBM therapy to a full year is the sole distinction. Variations in central nervous system (CNS) penetration are not taken into consideration by recommendations. Raising the dosage of rifampicin may lower mortality, according to recent trials conducted in people with TBM [13]. Fluoroquinolones penetrate the CNS quite well. It is yet unknown if fluoroquinolones are beneficial in TBM [14].

Results from adult TBM studies are beginning to show that greater doses of rifampicin were beneficial, and fluoroquinolones may help with TBM therapy. The Modified Rankin Scale (MRS) was utilized to assess functional status in children with TBM, and the effects of levofloxacin and rifampicin combined were examined. We modified the Mullen Scales of Early Learning (MSEL) instrument to evaluate neurocognitive state over an extended period of time.

MATERIALS AND METHODS

STUDY DESIGN AND PARTICIPANTS

We made contact with the families of hospitalized children who had plans for a lumbar puncture (LP) or who had signs of meningoencephalitis (such as fever, disorientation, or neurologic abnormalities). Parental interviews and reviews of medical records were used to gather clinical data. At screening, safety laboratory tests (full blood count, comprehensive metabolic panel), head computed tomography or magnetic resonance imaging, and CSF laboratory tests (cell count, glucose, protein; Gene Xpert; mycobacterial culture) were carried out. Consensus Research Definition was used to determine if a TBM was possible, likely, certain, or not [15]. Children had their illness severity staged using the Medical Research Council scale [16], their neurologic function evaluated by MRS [17], and their neurocognitive evaluation at admission evaluated by MSEL [18].

We included children diagnosed with TBM under the age of 15 in the current research. The age range for inclusion was 6 months to 15 years, weight more than 6 kg, and the consensus research case definition of probable or definite TBM (children with suspected TBM who were committed to TBM therapy by their treating doctors may also participate) [15]. Upon enrollment, children who had received more than 10 days of TB treatment, had a personal history of rifampicin-resistant TB, were expected to die within 24 hours, had a creatinine, alanine aminotransferase, or direct bilirubin level greater than 2, or had a human immunodeficiency virus with the intention of using protease inhibitors or nevirapine, were excluded.

RANDOMIZATION

The process of trial randomization involved the use of computer-generated centralization, resulting in a 1:1:1 allocation. The process of randomization was stratified based on the research site and age category, which was categorized into three groups: children aged less than 2 years, children aged 2 to less than 5 years, and children aged 5 to 12 years. The participants were randomly assigned to a treatment group and underwent an 8-week trial period when they got the treatment under direct observation.

STUDY TREATMENT AND PROCEDURES

All patients were administered isoniazid (H) and pyrazinamide (Z) at the recommended dosages. In arm 1, participants were administered high-dose rifampicin and ethambutol (HR30ZE). In arm 2, participants were given high-dose rifampicin and levofloxacin (HR30ZL). In arm 3, participants received standard-of-care treatment according to the World Health Organization recommendations (HR15ZE). The children were subjected to routine clinical exams and safety evaluations. The Modified Rankin Scale (MRS) assessments were conducted at three time points: week 8, week 24, and week 52. The Multiple Sclerosis Functional Composite (MSEL) assessment was conducted at both week 8 and at the conclusion of the trial, which occurred at either week 52 or week 72. The criteria for early termination of therapy, as stated by the protocol, encompassed many factors. These factors included the use of pharmaceuticals that were not permitted, drug toxicity that satisfied the criteria for permanent withdrawal of the drug, persistent nonadherence to the treatment regimen, or the diagnosis of tuberculosis that was resistant to the prescribed medication. At the start of the study, the participants were monitored for a duration of 72 weeks. However, as the investigation progressed and timetables for completion were considered, the follow-up period was subsequently shortened to 52 weeks.

STUDY ENDPOINTS

The main clinical measure used in this study was the Modified Rankin Scale (MRS), which ranges from 0 (indicating no symptoms) to 6 (indicating death) [17]. To ensure a more objective assessment of MRS values, we utilized the Gross Motor Function Classification System—Expanded and Revised. The primary focus of our safety analysis was on adverse events of grade 3 or higher, as defined by the Division of AIDS Grading Table, version 2.1, released in March 2017. As a secondary endpoint, we also measured the Mullen Scales of Early Learning (MSEL) score, which was adapted for local use and available in Hindi, Marathi, Tamil, or Chichewa. Both the overall score and subscale scores of the MSEL were recorded. Additionally, we documented the treatment outcomes of tuberculosis (TB) in our study.

RESULTS

BASELINE CHARACTERISTICS

25 children were enrolled, 75 were screened, and 98 were prescreened between June 2021 and May 2023. The slower-than-anticipated enrolment rate prevented the goal sample size from being met. Many children with a wide range of illnesses and causes for prescreening failure presented with neurologic symptoms, fever, or other indications for LP. Screening failure was most frequently caused by TBM diagnostic score less than 11. With a median age of 7.2 (IQR, 1–15) years, stage I, II, and III illness was present in 24%, 32%, and 24% of cases, respectively (Table 1). Of them, 13 (52%) had definite TBM. Less playfulness (81%), lethargy (65%), fever (61%), irritation (45%), stiff neck (41%), and altered awareness (33%) were among the common symptoms.

Table 1: Demographic and Clinical Information About Enrolled Participants, by Arm

Baseline Characteristic	Arm 1: R30HZE (n = 8)	Arm 2: R30HZL (n = 10)	Arm 3: R15HZE (n = 7)
Age, y, median (IQR)	7.5 (1–15)	6.7 (0.8–14.3)	7.2 (0.9–14.5)
Female sex	4 (50)	6 (60)	3 (42.8)
Weight, kg, median (IQR)	11.4 (6.5–23.2)	10.5 (6.1–20.3)	8.7 (7.3–21.6)
Head CT			
Normal	3 (37.5)	3 (30)	3 (42.8)
Abnormal	3 (37.5)	5 (50)	4 (57.1)
Not done	2 (25)	2 (20)	0
CSF laboratory tests, median (IQR)			
WBC count, cells/μL	78 (15–310)	67 (9–65)	72 (18–165)
Lymphocytes, %	81 (63–99)	75 (43–86)	76 (36–88)
Glucose, mg/dL	55 (23–69)	52 (28–73)	48 (34–71)
Total protein, g/dL	121 (61–239)	96 (67–165)	104 (56–123)
TBM classification			
Definite	5 (62.5)	5 (50)	3 (42.8)
Probable	2 (25)	3 (30)	3 (42.8)
Possible	1 (12.5)	2 (20)	1 (14.8)
Baseline Modified Rankin Scale score, median (range)	3 (1–4)	2 (1–4)	2 (1–4)
Stage			
I	2 (25)	3 (30)	1 (14.8)
IIA	2 (25)	3 (30)	3 (42.8)
IIB	2 (25)	2 (20)	2 (28.6)
III	2 (25)	2 (20)	1 (14.8)

EFFICACY OUTCOMES

In arms 1-3, the median (range) MRS scores at admission were 3 (1–4), 2 (1–4), and 2 (1–5), respectively. By week 8, all arms had shown rapid progress, and by week 24, nearly all of the kids had recovered to a score of 0 or 1, which indicates little to no handicap. The adjusted ratios of the likelihood of having a higher rather than lower MRS across the trial period were 2.85 (arm 2 versus arm 3) and 3.43 (arm 1 vs arm 3) when compared to SOC after controlling for age, sex, and baseline MRS.

After correcting for age and baseline MRS, children receiving high-dose rifampicin (arm 1) in neurocognitive tests showed statistically significant improvements in their longitudinal scores for fine motor, receptive language, and expressive language when compared to SOC (Table 2). Arm 1 showed a little but statistically significant improvement in neurocognitive outcomes over arm 2, with the exception of gross motor ability. Relapses or treatment failures were not noticed in any of the children.

Table 2: Neurocognitive Outcomes, Comparing the 3 Arms, Assessed Longitudinally Over the Course of Study Participation

Outcome Variable	Arm 1: $R_{30}HZE$ (n = 8)	Arm 2: $R_{30}HZL$ (n = 10)	Arm 3: $R_{15}HZE$ (n = 7)
Visual reception	3.45 (–2.42 to 5.98)	–1.92 (–4.51 to 4.45)	Ref
Fine motor	11.3 (3.67–19.2)	2.67 (–2.61 to 5.71)	Ref
Receptive language	9.2 (4.74–17.4)	4.30 (–1.68 to 9.28)	Ref
Expressive language	15.3 (5.35–23.8)	12.64 (–1.34 to 16.1)	Ref
Gross motor	5.15 (–1.40 to 9.50)	8.20 (–0.31 to 13.11)	Ref

SAFETY AND TOLERABILITY PROFILE

41% of participants experienced grade 3 or higher adverse events, which were common: 4 of 8 (50%) in arm 1, 6 of 10 (60%) in arm 2, and 3 of 7 (42.8%) in arm 3. Three in arm 1, one in arm 2 (also for toxicity), and one in arm 3 (disallowed drug) accounted for the six early treatment discontinuations. Only two of the four early treatment terminations due to toxicity happened during experimental therapy; the other two happened during the regular continuation phase of treatment. In the context of a serious illness marked by deteriorating CSF values, end organ damage (including liver destruction), and decreasing mental condition, there was just one fatality, in arm 1. Every other youngster finished the study.

DISCUSSION

The results of the first RCT using antibiotics to treat pediatric TBM are presented here. Unexpectedly, despite the fact that many of the trial participants had begun therapy for early stages of the disease, virtually all of the children performed well from a functional perspective, with the majority of them showing no physical deficits at the conclusion of the 8-week research period or during longer-term follow-up. We were unable to identify variations in functional result by treatment assignment because of the good functional outcomes across research arms and the small sample size. This may have been due in part to the MRS scale's limited ability to identify more subtle impacts on functional status. The majority of adverse events did not lead to an early termination of treatment, and those that did were equally likely to occur during the intensive phase of TBM (when experimental treatment was offered) as during the continuation phase (when SOC was provided to all children). Adverse events were common, as would be expected in a cohort of sick, hospitalized children receiving multidrug therapy for TBM. Significantly, compared to children receiving SOC dosage, children getting higher-dose rifampicin had significantly improved neurocognitive results in the areas of fine motor, receptive language, and expressive language. This conclusion has to be confirmed in a larger experiment. These results are in line with cohort studies that show positive results for kids on high-dose rifampicin-based regimens.

A treatment impact on neurocognitive outcomes was discernible. To be sure this is a legitimate discovery, larger trials will need to replicate the tiny sample size. Children with brain damage from TBM or other causes frequently experience "invisible disabilities" in addition to neurologic consequences because of the disease's or its treatment's influence on the growing brain. An significant characteristic of CNS TB is that M. tuberculosis replicates in microglia, which are important for neurodevelopment as well as immunological response to the pathogen [19]. Early therapy with higher-dose rifampicin appeared to enhance the neurocognitive results in the domains of fine motor, receptive language, and expressive language in children with TBM. Our research emphasizes the value of researching therapies in specific demographics as opposed to extrapolating results from adult trials when those trials' predicted outcomes are different. Our observational and trial studies indicate that children with TBM should undergo cognition testing and get full rehabilitation that includes speech and language therapy in addition to physical therapy and other specialized therapies [20].

Our trial has a few restrictions. First off, the desired sample size was not reached. Given the rarity of TBM in children and the considerable variation in disease presentation and response to therapy, informative translational studies along with a broad network of sites will be necessary to more thoroughly and effectively assess regimens for TBM. Second, because of the limited sample size, we were unable to draw firm conclusions about safety across arms. Other studies suggest that high-dose rifampicin has a largely positive safety profile in adults and children with pulmonary TB and TBM. In TBM, fluoroquinolones may be less safe; a meta-analysis found a greater risk of seizures or visual loss. Third, it's possible that the rifampicin dosage we used for our tests was too low. Fourth, it is difficult to evaluate neurocognitive outcomes using a single, uniformly administered instrument over a wide range of ages (0–12 years) and cultural contexts. Lastly, the fact that this trial was open-label might have contributed to bias. To enable precise dosage among children of all various ages, a placebo-controlled blinded experiment was not practical due to the high pill loads and the abundance of weight bands.

In conclusion, functional results were good across arms in this first-ever study of antimicrobials targeted for pediatric TBM. Children who received high-dose rifampicin had statistically superior neurocognitive results than those who did not; however, bigger

studies are needed to confirm this conclusion. A complete evaluation of the possible hazards and advantages of substituting levofloxacin with ethambutol was not possible due to the limited sample size, however there was no appreciable benefit of levofloxacin.

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