Safety and efficacy of levofloxacin versus rifampicin in tuberculous meningitis: an open-label randomized controlled trial

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Objectives: We report the efficacy and safety of levofloxacin versus rifampicin in tuberculous meningitis (TBM).

Patients and methods: In this open-label, randomized controlled trial from India, patients with TBM diagnosed on the basis of clinical, MRI and CSF findings were included. Patients with hepatic or renal dysfunction, organ transplantation, malignancy, pregnancy, lactation, allergy, seizure, age <15 years and antitubercular treatment ≥1 month were excluded. Sixty patients each were randomized to levofloxacin (10 mg/kg, maximum 500 mg) or rifampicin (10 mg/kg, maximum 450 mg). They also received isoniazid, pyrazinamide, ethambutol, prednisolone and aspirin. The primary outcome was death and secondary outcome measures were 6 month disability, repeat MRI changes and serious adverse events (SAEs).

Results: The median age of the patients was 34.5 (16–75) years. The baseline clinical and MRI findings were similar between the two groups. At 6 months, 13 out of 60 (21.7%) patients in the levofloxacin arm and 23 out of 60 (38.3%) patients in the rifampicin arm had died (P=0.07). On Cox regression analysis, survival in the levofloxacin group was significantly better than in the rifampicin group (hazard ratio 2.13, 95% CI 1.04–4.34, P=0.04). The functional outcome (P=0.47) was, however, not significantly different between the two groups.

On intention-to-treat analysis, 10 out of 47 (21.3%) in the levofloxacin arm and 5 out of 37 (13.5%) in the rifampicin arm had poor recovery. Repeat MRI findings did not differ between the groups. Levofloxacin was discontinued more frequently than rifampicin due to SAEs (16 versus 4, P=0.01).

Conclusions: Levofloxacin is superior to rifampicin in reducing 6 month death in TBM but not disability. Levofloxacin may be used in TBM especially in those patients with hepatotoxicity and without seizure.

Keywords: MRI, prognosis, antitubercular drugs, corticosteroids

Introduction

Tuberculous meningitis (TBM) occurs in 10% of patients with tuberculosis.1 It results in death or severe disability in nearly half of affected patients.2 The introduction of rifampicin and pyrazinamide has not resulted in further decline of mortality over isoniazid and streptomycin.3,4 Rifampicin is bactericidal but has poor CSF penetration.5 The concentration of rifampicin has been found to be below the MIC in two studies.6,7 The use of rifampicin in TBM is based on a few trials that are not class 1.8,9 The role of rifampicin in the treatment of TBM was highlighted in a study in which all patients resistant to isoniazid and rifampicin died, but only 28.7% died who were susceptible to antitubercular drugs.10 In a recent study, 450 mg of rifampicin orally resulted in a CSF concentration below the assay level (0.26 mg/L) in 64% of patients, whereas 600 mg of rifampicin intravenously resulted in a higher CSF concentration and only 4% were below the assay level. The higher dose of rifampicin in that study was associated with lower 6 month mortality without significant increase in hepatotoxicity.11

Besides the CSF penetration and efficacy of antitubercular drugs, the safety profile of the drug is also important. Drug-induced hepatitis is more common in Asians and has been reported in 26%–36% of patients.12,13 Of the first-line antitubercular drugs, isoniazid, pyrazinamide and rifampicin have hepatotoxic potential. In view of poor CSF penetration, hepatotoxicity and a paucity of strong evidence for the benefit of a standard dose of rifampicin in TBM, it is important to explore other antitubercular drugs. Of the candidate drugs, clarithromycin and fluoroquinolones have been tried in tuberculosis. The latter are more promising. Quinolones are bactericidal, have no hepatotoxicity and have been reported to be beneficial in multidrug-resistant tuberculosis.14 Moxifloxacin and levofloxacin have higher CSF penetration compared with other quinolones and have been evaluated...
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in a few studies as an add-on or alternative to ethambutol.\textsuperscript{10,11} In the present study, we therefore report the efficacy and safety of levofloxacin compared with rifampicin in patients with TBM.

**Methods**

**Study design**

This is an investigator-initiated, single-centre, open-label randomized controlled trial comparing the efficacy and safety of levofloxacin versus rifampicin in patients with TBM in addition to isoniazid, pyrazinamide and ethambutol. The study was conducted in a tertiary care teaching hospital in India. The protocol was designed by the first and second authors. Consecutive TBM patients admitted to the neurology service were enrolled from July 2009 to June 2012. The study was approved by the Local Ethics Committee (no. A-15.9PG/DM/IEC/50/13.4.2010) and was retrospectively registered in the Clinical Trial Registry, India (CTRI/2012/11/003155). The patients or their representatives gave informed consent. The sample size was calculated keeping the type I error $\alpha = 0.05$ and type II error $\beta = 0.15$ using Fisher’s exact test. We considered the absolute reduction in deaths in the levofloxacin arm as 15%. Death in the rifampicin arm was considered to be 40% based on the reported mortality in TBM.\textsuperscript{15,16} The required sample size was 64 in each arm.

**Inclusion criteria**

Patients with TBM were diagnosed on the basis of clinical, MRI and CSF findings. Essential criteria included the presence of meningitis symptoms consisting of fever, headache or vomiting for $\geq 2$ weeks in patients in whom malaria, septic and fungal meningitis were excluded. Supportive criteria included the following: (i) CSF cells $\geq 0.2 \times 10^9/L$ with lymphocytic predominance, protein $\geq 2$ g/L, sterile bacterial and fungal culture and absence of cryptococcal antigen; (ii) MRI evidence of exudates, hydrocephalus, infarction or tuberculoma; and (iii) extra-CNS tuberculosis.

The presence of essential criteria and any two of the supportive criteria was considered as TBM. The presence of acid-fast bacilli (AFB) in the CSF smear or culture, positive PCR or IgM antibody in the CSF was considered as TBM. The presence of acid-fast bacilli (AFB) in the CSF smear or culture, positive PCR or IgM antibody in the CSF was considered as TBM.

**Exclusion criteria**

Patients with seizures, liver or kidney failure, malignancy, long-standing immunosuppressive therapy, organ transplantation, pregnancy, lactation, age $< 15$ years and prior antitubercular treatment (ATT) for $\geq 1$ month were excluded.

**Evaluation**

Patients were subjected to detailed clinical evaluation. The duration of illness, presence of focal neurological deficit, seizure, evidence of raised intracranial pressure (hyperventilation and extensor posturing) and evidence of extra-CNS tuberculosis (lymph node, lungs, abdomen and bone and joint) were noted. Consciousness was assessed by the Glasgow Coma Scale (GCS). The presence of cranial nerve palsy was noted. Focal weakness was categorized into monoplegia, hemiplegia, paraplegia or quadriplegia. The meningitis was graded as follows: stage I, meningitis only; stage II, meningitis with focal neurological deficit or GCS score 11–14; or stage III, meningitis with GCS score $< 11$.\textsuperscript{18}

**Investigations**

Blood counts, erythrocyte sedimentation rate, haemoglobin, blood sugar, serum creatinine, albumin, bilirubin, transaminase and electrolytes were measured at admission and were repeated when required. Radiograph of the chest, electrocardiogram and HIV serology were performed in all patients. Cranial MRI was done using a 3T MRI scanner (Signa GE medical system, WN, USA). T1, T2, FLAIR, DWI and T1 contrast images were obtained in axial, coronal and sagittal planes. The presence of meningeal enhancement, granuloma, infarction and hydrocephalus was noted. Lumbar CSF was analysed for cells, protein and sugar and a CSF smear was examined for the presence of AFB. CSF BACTEC culture, PCR and IgM ELISA for Mycobacterium tuberculosis were also conducted.

**Randomization and treatment**

The patients were randomized to receive either 10 mg/kg/day rifampicin (maximum of 450 mg/day) or 10 mg/kg/day levofloxacin (maximum of 500 mg/day) using computer-generated random numbers in a 1:1 ratio. All the patients received 5 mg/kg/day isoniazid (maximum of 300 mg), 25 mg/kg/day pyrazinamide (maximum of 1500 mg) and 15 mg/kg/day ethambutol (maximum of 800 mg).\textsuperscript{19} The drugs were given orally in the conscious patients and through nasogastric tube in the unconscious patients after dissolving in 30 mL of plain water on an empty stomach and was followed by 20 mL of plain water. Subsequent treatment was decided by the treating physician. Patients also received 0.5 mg/kg prednisolone (maximum of 40 mg) for 1 month, which was then tapered over the next 4 weeks. All patients received 150 mg/day aspirin unless contraindicated. In patients with HIV, antiretroviral treatment was started after 1 month. Patients having hydrocephalus with raised intracranial pressure resulting in deterioration of consciousness had a ventriculoperitoneal shunt fitted. Patients were examined clinically twice daily and liver function tests were conducted weekly or earlier if indicated during the hospital stay. After discharge, patients were followed up at 1, 3 and 6 months or earlier if indicated and their outcome and any side effects of the drugs were recorded. Liver function tests (serum bilirubin, transaminase and alkaline phosphatase) were measured at 1 and 3 months or earlier if indicated. The cranial MRI was repeated at 6 months in the surviving patients per protocol and even earlier if clinically indicated.

**Serious adverse events (SAEs)**

Patients were observed for drug reaction, gastrointestinal symptoms, jaundice, encephalopathy, seizure, myoclonus and delirium. We used modified criteria of ATT-induced hepatitis as described by Ungo et al.\textsuperscript{20} The patients were considered to have ATT-induced hepatitis if there was a three times increase in transaminase in symptomatic (anorexia, nausea and vomiting) and five times increase in asymptomatic patients whose baseline liver function tests were normal.\textsuperscript{20} Serum creatinine $> 1.6$ mg/dL was considered as indicating impaired renal function. In patients with SAEs, the study drug was stopped and an alternative treatment was prescribed. The presence of isolated gastrointestinal symptoms was not an indication for stopping the study drug.

**Outcome**

The primary outcome measure was death at 6 months and the secondary outcome measures were disability, change in MRI at 6 months and SAEs. The functional outcome was defined on the basis of the 6 month Barthel index (BI) score [poor (BI $< 12$), partial (BI $= 12 - 19$) and complete (BI $\geq 20$)] recovery].\textsuperscript{2}

**Statistical analysis**

The baseline characteristics of the two study groups were compared using Fisher’s exact test for categorical variables and an independent $t$-test or Mann–Whitney $U$-test for continuous variables. Per-protocol and intention-to-treat analyses were conducted for death and functional outcome. Patients with SAEs were also followed up, although they were withdrawn from the study drug and their 6 month outcome was included in the group to which they were randomized. Patients lost to follow-up were included in the poor recovery group. Secondary outcomes were evaluated using Fisher’s exact test. Kaplan–Meier survival estimates were used
to display the survival of the patients who received levofloxacin or rifampicin. The relative risk of death between the levofloxacin and rifampicin groups was analysed using Cox regression analysis. At least one confounding variable per 10 deaths was adjusted and the variables having the lowest $P$ value in the univariate analysis were included. Variables were considered significant if the two-tailed $P$ value was $<0.05$. The statistical analysis was conducted using SPSS version 16.

**Results**

**Recruitment**

During the study period, 203 patients with TBM were screened, 120 of whom were randomized (Figure 1).

**Patient characteristics**

The median age of the patients was 34.5 (16–75) years and 53 (44.2%) were females. The baseline clinical, laboratory and imaging characteristics were similar in both groups (Tables 1 and 2). During the course of treatment, 17 out of 120 (14.2%) patients needed a ventriculoperitoneal shunt (9 patients in the levofloxacin group and 8 in the rifampicin group).

**Primary outcome**

At 6 months, 44 patients could be retained in the levofloxacin group and 56 in the rifampicin group. Levofloxacin had to be discontinued more frequently compared with rifampicin due to SAEs (16 versus 4, $P=0.01$). On per-protocol analysis, there were insignificantly more deaths in the rifampicin arm compared with the levofloxacin arm ($P=0.14$). Eleven out of 44 (25%) patients in the levofloxacin arm and 23 out of 56 (41.1%) in the rifampicin arm died. The functional outcome at 6 months was also insignificantly worse in the rifampicin arm compared with the levofloxacin arm (5/33 versus 1/33, $P=0.23$).

In 16 patients, levofloxacin had to be stopped due to SAEs and 2 of them were lost to follow-up. Of the remaining patients, two died, seven had poor recovery, three partial recovery and two complete recovery. Rifampicin had to be stopped in four patients and all of them recovered completely. The patients who were lost to follow-up were included in the poor recovery group and the remaining patients were included in their respective group for intention-to-treat analysis. On intention-to-treat analysis, death in the levofloxacin arm was insignificantly lower compared with the rifampicin arm [13 (21.7%) versus 23 (38.3%), $P=0.07$]. The details of per-protocol and intention-to-treat analyses are

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**Figure 1.** Study flow chart.
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Table 1. Comparison of baseline clinical characteristics in patients with TBM receiving levofloxacin or rifampicin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Levofloxacin (n=60)</th>
<th>Rifampicin (n=60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>39.3 ± 16.5</td>
<td>38.0 ± 18.5</td>
<td>0.42</td>
</tr>
<tr>
<td>Female</td>
<td>29</td>
<td>24</td>
<td>0.36</td>
</tr>
<tr>
<td>Duration of illness (weeks)</td>
<td>10.51 ± 9.36</td>
<td>11.11 ± 9.23</td>
<td>0.72</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7</td>
<td>7</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
<td>9</td>
<td>0.14</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>3</td>
<td>0</td>
<td>0.08</td>
</tr>
<tr>
<td>GCS score</td>
<td>11.8 ± 3.1</td>
<td>12.4 ± 3.2</td>
<td>0.31</td>
</tr>
<tr>
<td>Focal weakness</td>
<td>24</td>
<td>22</td>
<td>0.85</td>
</tr>
<tr>
<td>Extra-CNS tuberculosis</td>
<td>14</td>
<td>16</td>
<td>0.67</td>
</tr>
<tr>
<td>HIV positive</td>
<td>1</td>
<td>3</td>
<td>0.31</td>
</tr>
<tr>
<td>Stage of TBM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>9</td>
<td>12</td>
<td>0.70</td>
</tr>
<tr>
<td>II</td>
<td>33</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>18</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Laboratory and MRI findings in the patients with TBM receiving levofloxacin or rifampicin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Levofloxacin (n=60)</th>
<th>Rifampicin (n=60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF cells/mm³</td>
<td>183 ± 217</td>
<td>313 ± 822</td>
<td>0.96</td>
</tr>
<tr>
<td>protein (mg/dL)</td>
<td>192.4 ± 166.5</td>
<td>196.7 ± 167.9</td>
<td>0.75</td>
</tr>
<tr>
<td>glucose (mg/dL)</td>
<td>42.1 ± 31.9</td>
<td>47.4 ± 33.1</td>
<td>0.40</td>
</tr>
<tr>
<td>bacteriologically confirmed</td>
<td>18</td>
<td>24</td>
<td>0.17</td>
</tr>
<tr>
<td>serum bilirubin (mg/dL)</td>
<td>1.2 ± 1.5</td>
<td>0.92 ± 0.98</td>
<td>0.23</td>
</tr>
<tr>
<td>SGPT (U/L)</td>
<td>75 ± 96</td>
<td>86 ± 146</td>
<td>0.75</td>
</tr>
<tr>
<td>serum albumin (g/dL)</td>
<td>3.4 ± 0.7</td>
<td>3.4 ± 0.8</td>
<td>0.75</td>
</tr>
<tr>
<td>serum creatinine (mg/dL)</td>
<td>1.0 ± 0.5</td>
<td>0.9 ± 0.4</td>
<td>0.28</td>
</tr>
<tr>
<td>serum sodium (mEq/L)</td>
<td>132 ± 8.0</td>
<td>134.0 ± 8.0</td>
<td>0.15</td>
</tr>
<tr>
<td>MRI findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abnormal</td>
<td>54</td>
<td>51</td>
<td>0.58</td>
</tr>
<tr>
<td>exudate</td>
<td>25</td>
<td>22</td>
<td>0.62</td>
</tr>
<tr>
<td>hydrocephalus</td>
<td>25</td>
<td>26</td>
<td>0.86</td>
</tr>
<tr>
<td>tuberculoma</td>
<td>27</td>
<td>25</td>
<td>0.77</td>
</tr>
<tr>
<td>infarction</td>
<td>26</td>
<td>26</td>
<td>1.00</td>
</tr>
</tbody>
</table>

SGPT, serum alanine transferase.
aPositive AFB in smear/culture, IgM ELISA and PCR.

Discussion

In the present study, the survival of TBM patients at 6 months was significantly better in the levofloxacin arm compared with the rifampicin arm, although the functional outcome was not significantly different. The role of fluoroquinolones in the treatment of tuberculosis has been evaluated mostly in pulmonary tuberculosis. The efficacy of quinolones in TBM has been evaluated in two studies only. In one study in 61 patients with TBM, the role of ciprofloxacin, gatifloxacin and levofloxacin in addition to standard ATT was compared. The CSF penetration was maximal for levofloxacin followed by gatifloxacin and ciprofloxacin. There was a U-shaped response; the worst outcome was in the patients with the lowest and the highest plasma and CSF quinolone exposure compared with those with intermediate quinolone exposure. We therefore chose 500 mg/day levofloxacin to optimize the benefit based on its U-shaped response. Moreover, levofloxacin had to be withdrawn in 16 of our patients even at the dose of 500 mg/day due to seizure, myoclonus or encephalopathy. The higher incidence of seizures following levofloxacin in our study may be due to more severe meningitis or a genetic susceptibility.
The seizurogenic potential of quinolones has also been reported in earlier studies.24,25 MRI changes at 6 months were not significantly different between the levofloxacin and rifampicin arms. Only five patients developed infarction at follow-up, which is much lower than in our earlier reports in which 32%–40% of patients developed infarction after initiation of ATT.15,26,27 The lower frequency of infarction in the present study may be due to the use of both corticosteroid and aspirin. We used a relatively lower dose of corticosteroid compared with the study from Vietnam in which 0.3–0.4 mg/kg dexamethasone was used and tapered over 6–8 weeks. Long-term follow-up revealed insignificantly higher survival at 2 years but not at 5 years.28 In our earlier studies, we have used 10 mg/kg methyl prednisolone intravenously for 5 days in TBM and it did not result in improvement in clinical and in somatosensory and motor evoked potentials compared with those who were not on methylprednisolone.17,29 In the present study, therefore, we used a low dose of corticosteroid.

The limitations of the present study are that it is a single-centre study from a tertiary referral teaching institute and has an open-label design. A large number of patients could not be randomized due to seizure at presentation or already being on ATT. Moreover, in many patients, levofloxacin had to be withdrawn due to SAEs. It would have been better to exclude the patients with structural brain lesions, particularly in the frontotemporal region, because of potential for seizures especially if exposed to seizurogenic drugs. The present study is also underpowered. A multicentre study using levofloxacin as an add-on antitubercular drug is in progress.30 From this study, it can be concluded that levofloxacin in TBM results in better survival at 6 months compared with rifampicin, although disability was not different between the two groups. Levofloxacin may be used as an alternative drug to rifampicin especially in patients with hepatic dysfunction who do not have seizure.

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Transparency declarations
None to declare.
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Author contributions
J. K. was involved in protocol design, randomization, data analysis and writing the manuscript, U. K. M. was involved in planning the study and writing the manuscript, S. P. was involved in the clinical evaluation, follow-up and data collection and S. K. B. was involved in analysis of data.

References