Major outcomes of patients with tuberculous meningitis on directly observed thrice a week regime

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Abstract

Background: Revised National Tuberculosis Control Programme (RNTCP) of Government of India provides intermittent thrice-a-week directly observed treatment short course (DOTS) regimen. Objective: Assessments of all-cause mortality and nine-month morbidity outcomes of patients with tuberculous meningitis (TBM) on RNTCP regimen. Materials and Methods: We prospectively followed up patients registered with RNTCP center, with a diagnosis of TBM from January 1st, 2010 to December 31st, 2011. Morbidity was assessed using modified Rankin Scale (mRS). Results: We had 43 patients with median duration for follow-up of 396 days and that of survivors of 425 days. Two patients defaulted. Fourteen patients (32.5%) had mRS score of 4 to 6 and 29 had mRS of 0 to 3 after 9-month treatment. Severe disability was not related to any factor on logistic regression. Severe disability was seen in one patient (6.66%) among the 15 patients with stage 1, nine (37.5%) out of 24 patients with stage 2 and three (75%) out of 4 patients with stage 3 disease. Eight patients died (18.6%) of whom 4 died during the intensive phase and 4 during the continuation phase of RNTCP regimen. Mortality was independently related to treatment failure with adjusted Hazard ratio of 8.29 (CI: 1.38-49.78) (P = 0.02). One patient (6.66%) died out of the 15 patients with stage 1 disease, 5 (20.8%) out of 24 patients with stage 2 disease and 2 (50%) out of the 4 with stage 3 disease. Discussion and Conclusion: RNTCP regimen was associated with good compliance, comparable mortality and morbidity.

Key Words

Meningeal Tuberculosis, morbidity, mortality, prognosis, treatment

Introduction

Tuberculous meningitis (TBM) is associated with significant neurological sequelae, high morbidity[6,7] and a high mortality rate ratio of 1.79.[8] Most treatment guidelines of TBM even though not based on randomized controlled studies, recommend daily antituberculous agents (ATT) for 12 months.[9,10] Hence, most neurologists in India continue to give daily self-administered therapy for a variable period of 12 to 18 months, which incurs high out of pocket spending. The World Health Organization (WHO) also recommends daily regimen for 9 to 12 months and as an alternative have suggested directly observed intermittent ATT thrice a week for immune-competent patients during both intensive and continuation phases.

The Revised National Tuberculosis Control Programme (RNTCP) funded by Government of India gives intermittent thrice-a-week directly observed treatment short course (DOTS), both during intensive and continuation phases, for a total of 9 months for patients with TBM. We have been following this regimen for TBM in our institution from its inception.

There are very few reports on intermittent regimen in meningeal tuberculosis in adults.[8,9] Hence, we do not have evidence that the intermittent regimen is as good/superior/inferior to the daily regimen. We need follow-up studies in patients on intermittent regimen to guide national policies. Hence, we conducted a prospective study on patients with TBM on Government sponsored RNTCP regimen to look at the all-cause mortality, nine-month morbidity and the predictors for the same.

Materials and Methods

Setting

This study was undertaken by the Departments of Community Medicine and Neurology, Government Medical College Hospital, Thiruvananthapuram, Kerala, a tertiary care referral center in south India, after obtaining approval from
the Institutional Human Ethics Committee. Written informed consent was obtained from all the patients.

Subjects
We recruited consecutive patients registered to the RNTCP clinic at our center with a diagnosis of TBM from January 1\textsuperscript{st}, 2010 to December 31\textsuperscript{st}, 2011. We diagnosed TBM based on consensus tuberculous meningitis criteria and categorized them into definite, probable and possible TBM.\cite{10} We excluded patients below the age of 13 years and patients with Thwaites index of above four.\cite{10} Patients with a setting for bacterial meningitis like bacterial sinusitis, otitis media, cerebrospinal fluid (CSF) rhinorrhea and patients with history of head injury and nasal or aural bleeding were excluded. We excluded patients with pre-existing renal or liver disease, and immune-compromised patients including those with retroviral positive status. We also excluded patients with premorbid visual impairment, deafness and mental retardation since it would affect the morbidity assessment. We excluded patients who died within 5 days of initiation of RNTCP regimen since their early mortality is unlikely to have been influenced by the two doses of the RNTCP regime. All patients had chest radiographs, abdominal ultrasound examination, sputum acid-fast stain (AFB) stain, human immunodeficiency virus (HIV) serology, CSF analysis including AFB smear, mycobacterial cultures and neuroimaging of brain with contrast study.

Category 1 was initiated in previously unexposed patients and category 2 for patients exposed to antituberculous agents (ATT). In the RNTCP regimen, category 1 consists of isoniazid (H) 10 mg per kg, rifampicin (R) 10 mg per kg, streptomycin (S) 750 mg (or ethambutol 30 mg per kg for those with contraindications or cannot tolerate streptomycin) and pyrazinamide (Z) 35 mg per kg given thrice a week during the intensive phase for two months followed by isoniazid and rifampicin alone thrice a week for the next seven months in the continuation phase \(2\) (HRZS) \(3/7\) (HR) 3. Category 2 consists of isoniazid, rifampicin, streptomycin, pyrazinamide as in category 1, along with ethambutol (E) given thrice a week for two months followed by isoniazid, rifampicin, ethambutol, and pyrazinamide given thrice a week for the next one month during the intensive phase followed by isoniazid and rifampicin alone thrice a week for the next seven months in the continuation phase \(2\) (HRZS) \(3/1\) (HREZ) \(3/7\) (HR) 3. All patients received steroids in the initial four weeks of treatment.

Subjects came once a month during the duration of treatment and there after once every three months till December 31\textsuperscript{st} 2012. RNTCP clinic functions six days a week. In addition to this care givers were encouraged to contact the principal investigator (TI) by cellphone in case of any medical illness or life events. Discontinuation one month after initiation of ATT for more than 1 month is considered as default as per RNTCP. Patients were asked to report if there is anorexia, vomiting or high colored urine on days in which they were not taking rifampicin. Patients with such symptoms should have their liver enzymes tested and ATT stopped, if it is elevated more than 5 times the upper limit of normal.\cite{12}

Assessment
Information regarding mortality was obtained either from the family informing us on their own or from them when we enquire regarding their absence for a scheduled visit. Morbidity was assessed using modified Rankin Scale (mRS).\cite{11} Strokes due to TBM were diagnosed from history, clinical examination findings and neuroimaging.

Age at the onset of illness, gender, stage of disease, time (in days) to presentation to the hospital from symptom onset, time (in days) to treatment initiation from symptom onset, Thwaites index, treatment category, presence of associated tuberculoma, cerebral infarcts, cerebrospinal fluid (CSF) pleocytosis >200 cells/ml, elevated CSF protein >200 mg/dl, tuberculous radiculomyelitis (spinal arachnoiditis), concomitant alcohol use of >14 drink per week in male and >11 drink per week in women, diabetes, steroid use prior to treatment were assessed as variables, which could determine the outcomes (mortality and morbidity).

Statistical Analysis: Mortality rates were expressed in percentage. We used GraphPad Prism 5 and Statistical Package for the Social Sciences software (SPSS, version 11.0) for statistical analysis. We used Kaplan Meier curves for survival analysis and Cox regression for unadjusted and adjusted hazard ratios on predictors of mortality. Risk factor for morbidity was done using Chi square test for bivariable analysis and logistic regression for multivariable analysis.

Results
Forty-seven patients with a diagnosis of TBM were registered between January 1\textsuperscript{st}, 2010 and December 31\textsuperscript{st}, 2011. Two patients died within 5 days of starting RNTCP regimen and 2 were lost for follow-up [Figure 1]. The last (43\textsuperscript{rd} patient) was recruited on 7/12/2011 and his treatment was completed on 10/9/2012. We had two patients with definite, 23 patients with probable and 18 patients with possible TBM as per the consensus criteria. The baseline characteristics are given in Table 1. Age at presentation ranged from 14 to 61 years. Majority had stage 2 disease [Table 1] Excess alcohol use was seen in 13 out of 22 male patients and none among the 21 females. Sixteen patients (37.2%) had cranial nerve deficits, 14 (32.6%) had arteritis, 9 (20.9%) had hydrocephalus, 7 (16.3%) had seizures, 5 (11.6%) had tuberculoma, 3 (7%) had spinal arachnoiditis, and 1 (2.3%) had caries spine during the hospital stay.

Thirteen patients (30.2%) had indirect evidence of tuberculosis elsewhere in the body. Chest radiograph was abnormal in 11 patients (25.6%). Milliary motting was seen in 2 patients, upper zone lesions in 5 patients, hilar adenopathy in 2 patients.
and lower zone lesions in 2 patients. One patient with lower zone lesion and another patient with miliary lesions on chest radiograph had documented splenomegaly. One patient had hydronephrosis due to tuberculous pyelonephritis. Another patient had supraclavicular lymphadenopathy, and ultrasound showed multiple conglomerate lymph nodes in celiac region with multiple large nodes in aorto caval, retrocaval and para-aortic region. We did CSF polymerase chain reaction (PCR) in 4 patients, out of which 2 were positive. We did CSF AFB smear and culture in all our patients but all turned out to be negative.

Two patients (40%) had seizures out of the 5 TBM patients with associated tuberculoma. In contrast, only five patients (13.1%) had seizures out of 38 TBM patients without tuberculoma. None of the TBM patients with tuberculoma died. The tuberculoma disappeared in all within 9 months of treatment except for one patient, who had to be given ATT for 12 months for the complete disappearance of tuberculoma.

All were on category 1 RNTCP regimen except two patients who were on category 2. All patients took injection streptomycin. Thirty-five patients (81.4%) completed full 9 month treatment. ATT was inadvertently stopped after 6 months in 3 and after 7 months in 2 patients by the RNTCP DOTS providers. One patient who was given ATT for only 7 months and did not take medication for a period of 38 days, comes under the definition of default. We had another patient who defaulted (after 4 month ATT) following development of hepatitis. ATT was given for 12 months for a patient with associated tuberculoma and for 15 months for a patient with spinal arachnoiditis. The median duration of follow-up of the entire cohort (both dead and surviving) was 396 days and that of survivors alone was 425 days.

Eight patients (18.6%) had paradoxical reaction in the form of increase in size of existing tuberculoma or development of new tuberculoma, out of whom 2 died and 5 had severe morbidity (mRS 4 to 6). Four patients (9.3%) developed treatment failure, three during the fourth month and one patient (INH resistant open case of pulmonary tuberculosis) during the ninth month of ATT. One patient who completed 9 month RNTCP regimen had relapse of meningitis 3 months after stopping medication and he responded to standard daily regimen of ATT.

Four patients (9.3%) developed hepatitis, one patient at the end of a month, two patients at 4 months and one patient at 7 months. All 4 of them had anorexia and one patient had vomiting too.

Eight patients (18.6%) died during the follow-up and had a median duration of follow-up of 74 days [Figure 2]. Majority (7/8) died within 5 months of initiation of treatment. Four died during the intensive phase and the rest four died during the continuation phase. There were no deaths during the post treatment follow-up period. The cause of death was not verified by autopsy. Interview by the principal investigator (TI) of the care givers of patients, who died, suggested TBM or its complications as the most likely cause. All 4 patients who died within 3 months of starting treatment had arteritis, but only 1 out of the 4 patients who died after 3 months treatment had arteritis \( (P = 0.1429) \). Three out of the 4 patients who died after 3 months of RNTCP regimen had relapse of meningitis. These 3 who died after 3 months of RNTCP regimen and one of the 4 patients who died within 3 months of RNTCP regimen had hydrocephalus \( (P = 0.4857) \). One person who died 3 months after starting RNTCP regimen had pre-existing psychosis and died of seizure and aspiration pneumonia. Two out of the 4 patients who died 3 months after starting RNTCP regimen were on category 2. One patient (6.66%) out of the 15 patients with stage 1 disease, 5 (20.8%) out of 24 patients with stage 2 disease and 2 (50%) out of the 4 with stage 3 disease died.

Kaplan Meier survival analysis showed that the mortality was related to hydrocephalus, drug resistance, treatment failure, category 2 treatment and arteritis [Table 2]. Treatment failure was the only significant variable with adjusted Hazard ratio of 8.29 (CI: 1.38-49.78) \( (P = 0.02) \) on Cox regression.

Fourteen patients (32.5%) died or had severe disability (mRS 4 to 6) and 29 had mild to moderate disability (mRS 0 to 3) at 9 month treatment. Severe disability was seen in one patient (6.66%) among 15 patients with stage 1, nine (37.5%) out of 24 patients with stage 2 and 2 (50%) out of the 4 with stage 3 disease died.

| Table 1: Baseline characteristics of 43 patients with Tuberculous meningitis |
|-----------------------------------|-----------|-----------|-------------|-------------|
| Patient characteristics | Dead (8 pts) | Alive (35 pts) | Total (43 pts) | mRS score 4 to 6 (13 pts) | mRS score 0 to 3 (30 pts) |
| Median age in years (IQR)* | 29 (21.75,45.75) | 39 (23.48) | 36 (23.48) | 42.00 (24.50,54.00) | 35.50 (22.75,45.75) |
| Male : Female | 6 : 2 | 16 : 19 | 22 : 21 | 9 : 4 | 13 : 17 |
| Duration of illness in median days (IQR) | 46.5 (13.75,118.3) | 15 (8, 32) | 17 (8, 62) | 31 (11,91) | 15 (7.75,32) |
| Time to treatment initiation in median days (IQR) | 51.5 (18, 121.3) | 22 (15, 40) | 25 (15, 65) | 39 (13.5, 96.5) | 21.50 (15, 40) |
| Stage 1 disease | 1 | 14 | 15 | 1 | 14 |
| Stage 2 disease | 5 | 19 | 24 | 9 | 15 |
| Stage 3 disease | 2 | 2 | 4 | 3 | 1 |
| Follow up duration in median days (IQR) | 74.00 (23.25, 131.3) | 425.0 (373, 565.0) | 396.0 (274, 544.0) | 137 (45.5,432.5) | 425 (328.5, 577) |

*interquartile interval, †-modified Rankin Scale, pts = patients

![Figure 2: Kaplan Meier curve](image-url)
24 patients with stage 2 and three (75%) out of 4 patients with stage 3 disease. Spinal arachnoiditis was seen in 2 of our patients with mRS 4 to 6 and in one among those patients with mRS of 0 to 3.

Severe disability was related to stage 2 and 3 disease, Thwaites index of ≥ 2, paradoxical reaction, and history of contact with pulmonary tuberculosis [Table 3]. But none of the above factors were significant on logistic regression.

We found that through the RNTCP programme patients were getting the directly observed medication except in one case during the intensive phase, which was indirectly rectified with the intervention of the RNTCP officer. The other case was also not directly observed and she was readmitted with meningitis and hydrocephalus 3 months after the initiation of ATT and she died on the 16th day of hospitalization. Out of the six patients where ATT was inadvertently stopped prior to completion of 9 month therapy, 5 were due to lack of awareness of RNTCP field staff regarding the duration of treatment for TBM. The sixth patient stopped ATT after 124 days due to drug induced hepatitis. None of these 6 patients had treatment failure, relapse or mortality during the study period.

**Discussion**

Current work is unique from other studies of TBM[14,15], in that it was prospective, had only adult patients and all were on intermittent thrice a week DOTS.

The mortality rate in our study (18.6%) was similar to the studies with daily regimen (17 to 43%).[3,16-19] Our observation of mortality during the continuation phase is consistent with the studies with daily regimen (29 to 60%).[3,16-19] In a retrospective study, the mortality was 17% and morbidity 13% at the end of 6 months with daily treatment.[19] In another study, at nine-month follow-up, 29% patients with TBM had either died or had severe disability.[18] Yet another study showed 22% mortality, 13% severe and 12% moderate disabilities.[3]

Even though the association with stage of disease and morbidity is well known[27,31], the association of severe disability with paradoxical reaction, Thwaites index and history of contact with pulmonary tuberculosis patient as shown by our study is novel. Duration of illness prior to admission[27], extra-meningeal tuberculosis[28], cranial nerve palsy[28,32], focal neurological deficits[29], drowsiness[28] and hydrocephalus[29] are also documented to be associated with poor outcome. Kalita et al. has shown that infarct, Glasgow coma scale, and stage of meningeal tuberculosis predict the outcomes at 6 and 12 months of follow-up.[14]

There are many causes for deterioration during the initial 6 weeks of daily ATT, which include development of hydrocephalus, infarcts, exudates and granulomas.[30] We found mortality to be associated with hydrocephalus, drug resistance, treatment failure, arteritis and category 2 treatment on bivariate analysis. Hydrocephalus[21,22], isoniazid resistance[23], increasing age,[21,24-26] duration of illness at the time of admission[27], delayed treatment[28], altered consciousness[29,30], stage III at presentation[27,30], convulsions[29], lower CSF lymphocytes[29], low CSF glucose[29] low CSF/blood glucose ratio[30], high protein levels[30], computerized tomography (CT) scan abnormality[30], HIV positivity[24,25], disseminated tuberculosis[29], excess alcohol use[24], black race[25], absence of corticosteroid use[24], no treatment supporters[25] and residence in a nursing home[24], are known to be associated with higher mortality.

One-third (32.5%) of our patients either died or had severe morbidity, which is similar to the prevalence in patients on daily regimen (29 to 60%).[13,16-19] In a retrospective study, the mortality was 17% and morbidity 13% at the end of 6 months with daily treatment.[19] In another study, at nine-month follow-up, 29% patients with TBM had either died or had severe disability.[18]

| Table 2: Risk factors for death |
|--------------------------------|
| **Risk factors** | **Died (8)** | **Alive (35)** | **P value** | **Hazard ratio (95% CI)** |
| Hydrocephalus | 4 (50) | 5 (14.29) | 0.043 | 4.187 (1.045 to 16.777) |
| Drug resistance | 1 (12.5) | 0 (0) | 0.040 | 9.990 (1.116 to 89.399) |
| Treatment failure | 3 (37.5) | 1 (2.86) | 0.005 | 10.184 (2.036 to 50.948) |
| Category 2 | 2 (25) | 0 (0) | 0.012 | 7.945 (1.585 to 39.821) |
| Arteritis | 5 (62.5) | 9 (25.71) | 0.042 | 4.416 (1.052-18.546) |

* = Confidence interval

| Table 3: Risk factors of severe disability |
|------------------------------------------|
| **Risk factors** | **mRS(13) 4 to 6** | **mRS(30) 0 to 3** | **P value** | **Odd ratio (95% CI)** |
| Stage 2 & 3 at presentation | 12 | 16 | 0.0166 | 10.50 (1.207 to 91.32) |
| Thwaites index ≥ 2 | 5 | 3 | 0.0415 | 5.625 (1.097 to 28.85) |
| Paradoxical reaction | 5 | 3 | 0.0415 | 5.625 (1.097 to 28.85) |
| History of contact with PT | 1 | 13 | 0.0329 | 1.090 (0.1251 to 0.9493) |

* = modified Rankin Scale, † = Confidence Interval
the presence of tuberculoma necessitated duration of treatment >9 months till the tuberculoma disappeared.

The main advantage of the RNTCP regimen is the associated good compliance, which has an important influence on the mortality and morbidity. We found that there is a need to increase the awareness of duration of treatment for TBM among the RNTCP DOTs providers. A good liaison between the treating Neurologist or the Physician with the DOTs provider is essential in the treatment of TBM because of the special issues of paradoxical reactions, recurrence of meningitis and decision on duration of treatment in case of patients with associated tuberculomas. We found that there was flexibility within the RNTCP programme in which we could ask for extension of intensive phase in genuine cases for a month. This was also true for extension of continuation phase if the associated granuloma has not completely subsided.

The strength of the study is that it was a prospective study of patients with TBM on intermittent regime with a reasonable follow-up documenting the mortality and morbidity. Our study has shown that some patients die following treatment failure both during the intensive as well as continuation phase after an initial response as with any regimen for TBM. The limitation of the current study is that very few were definite cases of TBM. Both patients on category 2 with history of exposure to ATT initially responded but had relapse of meningitis and died probably due to drug resistance. We have not systematically looked at drug resistance in our patients even though we presume that multi-drug resistant tuberculosis might be contributing to the mortality at least in some cases. Even though drug resistance is a risk factor for increased mortality,[23] there are contrary reports that isoniazid and streptomycin resistance do not increase the risk of death.[38] The fact that one patient who had relapse of meningitis after completion of 9 months of RNTCP regimen and responded to restart of intensive phase of daily regimen points to the fact that daily regimen still worked when there was relapse after completion of intermittent regimen.

Overall, RNTCP regimen was associated with good compliance, comparable mortality and morbidity. Only randomized controlled studies will tell us, if there is a difference between daily regimen and of intermittent thrice a week regimen on the mortality and morbidity of patients with TBM. However, as with other regimen, there was treatment failure and case fatality, which points to the search for better regimen and to designing newer drugs. This is especially true in the context of suspected emerging drug resistance.

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