Role of aspirin in tuberculous meningitis: A randomized open label placebo controlled trial

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A B S T R A C T
Objective: To evaluate the efficacy and safety of aspirin in preventing stroke and mortality in tuberculous meningitis (TBM).

Methods: Patients with TBM diagnosed on the basis of clinical, MRI and cerebrospinal fluid (CSF) criteria were randomized into aspirin 150 mg daily or placebo. All the patients received four drug antitubercular treatment- RHZE (rifampicin, isoniazide, pyrazinamide and ethambutol) with or without corticosteroid. The primary endpoint was MRI proven stroke at 3 months and secondary end points were mortality and functional outcome assessed by Barthel Index score at 3 months. The adverse drug reactions were also analyzed.

Results: 118 TBM patients were randomized into aspirin and placebo groups. The baseline demographic, clinical (severity of meningitis, MRI and CSF changes) were not significantly different between the two groups. 19 (16.1%) patients lost from follow up. 21 (33.3%) patients developed stroke after randomization which was insignificantly lesser in aspirin (24.2%) compared to the placebo group (43.3%; OR 0.42, 95%CI 0.12-1.39). Aspirin resulted in absolute risk reduction of stroke in 19.1% and significant reduction in mortality compared to placebo (21.7% Vs 43.4%, P = 0.02). On binary logistic regression analysis, the age (OR 1.09, CI 1.03-1.14, P = 0.001) was the only independent risk factor of stroke and aspirin was significantly related to survival (OR 3.17, 95% CI 1.21-8.31). Aspirin was well tolerated and was not withdrawn in any patient because of side effects.

Interpretation: Aspirin resulted in insignificantly lesser strokes and significantly reduced 3 month mortality in patients with TBM.

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1. Introduction

Tuberculosis affects one third of the world population and is one of the leading causes of mortality and morbidity. Amongst those aged 5 years or more, tuberculosis kills more people than AIDS, malaria, diarrhea, leprosy and all the tropical diseases combined. Tuberculosis results in 2 million deaths annually and 96% of those deaths occur in the developing countries of Asia and Africa [1]. Because of HIV pandemic, tuberculosis has become important in those areas where it was hitherto not important. Tuberculous meningitis (TBM) is the most severe manifestation of tuberculosis and is associated with exudates, tuberculosis, hydrocephalus and stroke. Small and medium size intracranial vessels are usually affected. Penetrating vessels develop endarteritis whereas vessels surrounded by exudates develop periarteritis which later may produce panarteritis [2,3]. Vasculitis in TBM has been reported in 41% in an autopsy study [4]. The frequency of infarct on CT scan studies varies from 17% to 64% [5,6] and on MRI 45% to 50% patients [7,8]. Vasculitis in TBM can result in infarctions which are typically located in the basal ganglia, mostly in the middle cerebral arterial territory and is associated with poor outcome [8-12]. Prevention or reduction of infarction may result in lower mortality and better outcome. Dexamethasone has an anti-inflammatory affect and may favorably influence the vasculitis in TBM. Administration of dexamethasone in TBM however did not result in reduction in occurrence of hemiplegia and paraplegia [13]. In another observational study on 43 patients with TBM, 24 received dexamethasone and the frequency of infarction in dexamethasone group was 27% compared to 58% in the placebo group although the difference did not achieve statistical significance [14]. In children with TBM, a prothrombotic state as evidenced by reduced protein S, and increased factor VIII and plasminogen activator inhibitor 1 have been reported which were more pronounced in stage III compared to stage II meningitis. The therapeutic measures that reduce the risk of thrombosis could therefore be potentially beneficial in TBM [15]. Aspirin has antiplatelet, antiaggregant, anti-inflammatory and anti-oxidant properties [16-18] and is most widely used as an antiplatelet drug for prevention of ischemic stroke [19]. In spite of high frequency
of stroke in TBM, the role of aspirin in preventing stroke has not been studied. In this communication, we report the results of a randomized open labeled placebo control trial evaluating the role of aspirin in preventing ischemic stroke in patients with TBM.

2. Subjects and methods

2.1. Inclusion criteria

The patients with TBM diagnosed on the basis of clinical, CSF and radiological criteria during 2005 to 2008 were included. The study was duly approved by the local ethics committee and patients or their relatives gave informed consent.

2.2. Diagnosis of TBM

The criteria for diagnosis of TBM were as follows:

Essential criteria: Meningeal symptoms comprising of fever, headache and vomiting for 2 weeks or more in whom malaria, septic and fungal meningitis were excluded.

Supportive criteria: 1) CSF pleocytosis with lymphocytic predominance, raised protein and sterile bacterial or fungal culture. 2) CT scan or MRI evidences of exudates, infarction, hydrocephalus or tuberculosis in isolation or in various combinations. 3) Evidence of extra CNS tuberculosis and 4) Response to antitubercular treatment.

Presence of essential and 3 of the 4 supportive criteria were considered highly probable and 2 supportive criteria as probable TBM. Presence of AFB in CSF smear or culture, positive CSF PCR or IgM ELISA for AF8 were considered as definite evidences of TBM [20].

2.3. Exclusion criteria

The patients on antitubercular treatment for more than 8 weeks and those with acid peptic disease, gastric hemorrhage, bleeding diathesis, aspirin allergy, liver or kidney failure, subarachnoid hemorrhage, underlying heart disease, major surgery within 2 weeks, pregnancy, enrolment in any other trial and associated malignancy were excluded.

2.4. Evaluation

The patients were subjected to detailed medical history and clinical examination. History of tubercular contact, BCG vaccination, past history of tuberculosis, immunosuppressive medications and presence of diabetes, HIV and hypertension were noted. The duration of illness, severity of symptoms including seizures and treatment were recorded. The level of consciousness was assessed by Glasgow Coma Scale (GCS). Presence of cranial nerve palsy and focal weakness (hemiplegia, paraplegia) were noted. The muscle weakness was categorized into complete or partial. Muscle tone and reflexes were categorized into normal, increased or reduced. Evidence of tuberculosis out side the CNS such as lung, lymph node, bone and joint was noted. The severity of meningitis was graded into

Stage I: meningitis only
Stage II: meningitis with focal signs
Stage III: Meningitis, focal weakness and altered sensorium [20].

2.5. Investigations

Hemoglobin, blood counts, erythrocyte sedimentation rate, HIV serology and serum chemistry including serum bilirubin, transaminases, creatinine, protein, albumin and electrolytes were estimated in all the patients. Radiograph of chest in posterior anterior view and electrocardiogram were carried out. Cerebrospinal fluid (CSF) was examined for opening pressure, protein, cell, glucose, and microscopy for bacteria, acid fast bacilli (AFB) and fungi. BACTEC culture of CSF was done for detection of AFB. Cerebrospinal fluid was also subjected to polymerase chain reaction (PCR) and IgM ELISA for mycobacterium TB.

Cranial MRI was performed using 1.5 T Signa GE Medical System Milwaukee, WN, USA. T1, T2, FLAIR, DW1 and T1 contrast sequences were carried out. Presence of exudates, tuberculoma, infarction and hemorrhage were noted. Hydrocephalus and periventricular signal alterations were also recorded. Cranial MRI was repeated if indicated by the clinical condition or at 3 months follow up.

2.6. Randomization

The eligible patients were randomly assigned to aspirin 150 mg (per oral or through nasogastric tube) or placebo though not double blind manner. The randomization was done using computer generated random numbers.

The patients were treated with 4 drug antitubercular RHZE regimens (rifampicin 10 mg/kg; isoniazide 5 mg/kg, pyrazinamide 25 mg/kg and ethambutol 15 mg/kg) per oral daily. All the drugs were continued for 9 months followed by RHE for 3 months and HE for another 6 months. Prednisolone 0.5-1.0 mg/kg, or dexamethasone 0.4 mg/kg was prescribed only to those who had ependymalopathy, raised intracranial pressure (ICP), herniation or impending visual failure. It was given for 4 weeks and tapered over next 4 weeks. Ventriculoperitoneal shunt was carried out in those with hydrocephalus with deteriorating consciousness. In the patients with communicating hydrocephalus, repeated lumbar punctures were performed and the clinical response was considered before the ventriculoperitoneal shunt surgery was performed.

2.7. Outcome measure

The primary outcome was occurrence of stroke on MRI at 3 months with or without clinical evidence of focal deficit. We have relied on MRI evidences of stroke, because focal deficit in TBM may as well occur due to tuberculoma or arachnoiditis. Moreover, the focal deficit may not be reported by the patients who are in altered sensorium. The secondary outcome measures included a) death and b) functional outcome at 3 months as assessed by Barthel Index (BI) score on a 0 to 20 scale. The recovery was categorized into complete (BI score = 20), partial (BI = 12 to 19) and poor (BI <12) [12]. Adverse drug reactions such as pain abdomen, gastrointestinal hemorrhage, allergy, ecchymosis, purpura, jaundice and liver function abnormalities were noted.

2.8. Statistical analysis

The sample size was calculated considering the prevalence of stroke in TBM to be 30%, the response variable as dichotomous, assuming type I error (α = 0.05), power of test (1-β = 0.80) and effect size of treatment 20%, the number of patients in each group was estimated to be 59. The baseline demographic (age, sex), clinical (duration of illness, focal weakness, cranial nerve palsy, GCS score, stage of meningitis), laboratory (CSF protein, cell, sugar), CT/MRI findings (exudates, hydrocephalus, granuloma, infarction) in the study and control group were compared. The categorical variables were compared by Chi square or Fisher’s exact test and continuous variables by Independent ‘t’ test or Mann-Whitney U test. The occurrence of stroke at 3 months in control and study groups was compared by Chi square test, and odds ratio (OR) with 95% confidence interval (CI) was calculated. Occurrence of stroke in those with and without exudates was also compared. The frequency of stroke in those with and without stroke before randomization was also compared to evaluate the role of aspirin in primary and secondary prevention. The
secondary outcome variables such as mortality, functional outcome and adverse events in the study and control groups were also compared. The relative risk, absolute risk reduction and number needed to treat (NNT) were also calculated. Univariate analysis was done to define the predictors of stroke and mortality. The variables which has a p value of ≤0.1 on univariate analysis were included together in binary logistic regression (forward) analysis and the final model predicting the stroke was derived. The same analysis was used for predicting the mortality. The statistical analysis was done using SPSS 15 version and Epilinfo statistical package. The variables were considered significant in univariate analysis if P value is ≤0.05.

3. Results

During the study period 149 patients with TBM were admitted. 31 patients were excluded due to prior antitubercular treatment for more than 2 months in 22, lack of consent in 5, liver or kidney failure in 2, hemorrhagic stroke in 1 and gastric hemorrhage in 1 patient. Therefore 118 patients were randomized into the aspirin and placebo groups (Fig. 1). The median age of the patients was 30 (range 6-82) years, 6 were children (≤12 years) and 60 were women. The median duration of illness was 6 (range 1-60) weeks. 63 patients were already on ATT for a mean duration of 13 days. The diagnosis of TBM was definite in 25, highly probable in 62 and probable in 31 patients. Extra CNS tuberculosis was present in 38 patients and included pulmonary TB=Tuberculosis. CNS=central nervous system, CSF=Cerebrospinal fluid, TB=Tuberculosis.

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33 (28%) patients died; 26 during hospital stay and 7 after discharge before the follow up MRI was scheduled. In 3 patients, MRI could not be repeated due to financial constraint. 19 (16.1%) patients lost from follow up. Repeat MRI therefore was possible at 3 months in 32 (miliary in 12) and bone and joint tuberculosis in 2 patients. The seizures were present in 38 patients. The median GCS score was 13 (range 3-14) and 86 patients had altered sensorium.

59 patients each received aspirin or placebo. The demographic, clinical variables (severity of meningitis, GCS score), CSF findings, radiological findings, number of patients on steroid therapy, association of comorbidities such as diabetes, hypertension, extra CNS tuberculosis, shunt surgery and duration of antitubercular treatment before randomization were not significantly different between the two groups (Table 1). The base line characteristics of the patients receiving only aspirin or corticosteroid, corticosteroid and aspirin and those neither received corticosteroid nor aspirin are shown in Table 2.

4. Outcome measures

4.1. Primary outcome

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<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Placebo (N=59)</th>
<th>Aspirin (N=59)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>15 (55.5%)</td>
<td>10 (58.8%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Highly probable</td>
<td>16 (59.3%)</td>
<td>13 (76.5%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Possible</td>
<td>6 (22.2%)</td>
<td>2 (11.8%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Age</td>
<td>30.1 ± 14.3</td>
<td>25.5 ± 14.2</td>
<td>0.008</td>
</tr>
<tr>
<td>GCS score (mean ± SD)</td>
<td>12.6 ± 3.1</td>
<td>11.9 ± 3.1</td>
<td>0.85</td>
</tr>
<tr>
<td>Duration of symptoms (mean ± SD) weeks</td>
<td>8.3 ± 4.3</td>
<td>9.6 ± 11.5</td>
<td>0.79</td>
</tr>
<tr>
<td>Stroke at presentation</td>
<td>3 (11.1%)</td>
<td>4 (23.5%)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

GCS = Glasgow Coma Scale.
received aspirin nor corticosteroid. The details are shown in the Table 3. On univariate analysis, the variables having $P \leq 0.1$ included age ($P=0.001$) and hydrocephalous ($P=0.08$). The details are shown in Table 4. On binary logistic regression analysis the age (OR 1.09, CI 1.03–1.14, $P=0.001$) was the only independent risk factor of stroke.

### 4.2. Secondary outcome

33 (28%) patients died and the possible causes of death could be ascertained in 26 patients who died during the hospital stay. 15 patients died due to septicemia and pneumonia and 11 due to raised intracranial pressure. 10 (21.7%) patients died in the aspirin and 23 (43.4%) in the placebo groups which was significantly higher in the placebo group (OR 2.76, 95%CI 1.05–7.39, $P=0.03$). The absolute risk reduction following aspirin was 22% and NNT of 9.8 and there was no difference in 3 months functional outcome compared to those without (40%; $P=0.05$). The details are shown in Fig. 2. On univariate analysis, the mortality was significantly related to stage of meningitis ($P=0.01$), GCS score (OR 0.82, 95% CI 0.70–0.97). At 3 months, 31 patients had complete, 24 partial and 42 poor recovery. Aspirin did not result in significant difference in 3 months functional outcome ($P=0.16$). The relationship of new stroke, mortality and functional outcome with different treatments groups is shown in Fig. 3.

### Table 3

The relationship of occurrence of stroke and mortality in patients with tuberculous meningitis receiving only steroid or aspirin, both aspirin and steroid, and placebo only.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Died (N = 33)</th>
<th>Survived (N = 66)</th>
<th>P value</th>
<th>Stroke (N = 21)</th>
<th>No stroke (N = 42)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin only</td>
<td>8 (33.3%)</td>
<td>16 (66.7%)</td>
<td>0.60a</td>
<td>4 (26.2%)</td>
<td>11 (73.3%)</td>
<td>0.18a</td>
</tr>
<tr>
<td>Steroid only</td>
<td>8 (47.1%)</td>
<td>9 (52.9%)</td>
<td>0.63b</td>
<td>2 (20.0%)</td>
<td>8 (80.0%)</td>
<td>0.15b</td>
</tr>
<tr>
<td>Steroid + aspirin only</td>
<td>3 (13.0%)</td>
<td>20 (87.0%)</td>
<td>0.05c</td>
<td>4 (22.2%)</td>
<td>14 (77.8%)</td>
<td>0.08c</td>
</tr>
<tr>
<td>Placebo only</td>
<td>14 (40.0%)</td>
<td>21 (60.0%)</td>
<td>0.550</td>
<td>11 (55.0%)</td>
<td>9 (45.0%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4

Relationship of various variables with occurrence of stroke in the patients with tuberculous meningitis.

<table>
<thead>
<tr>
<th>Age (mean ± SD)</th>
<th>Stroke (N=21)</th>
<th>No stroke (N=42)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>41.19 ± 15.1</td>
<td>27.3 ± 11.6</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>9 (42.9%)</td>
<td>22 (57.1%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td>0.85</td>
</tr>
<tr>
<td>I</td>
<td>7 (33.3%)</td>
<td>17 (66.7%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>12 (57.1%)</td>
<td>21 (42.9%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>5 (23.8%)</td>
<td>9 (76.2%)</td>
<td></td>
</tr>
<tr>
<td>GCS score (mean ± SD)</td>
<td>12.29 ± 2.7</td>
<td>13.12 ± 2.7</td>
<td>0.25</td>
</tr>
<tr>
<td>Focal weakness</td>
<td>2 (9.5%)</td>
<td>7 (30.4%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Extra CNS TB</td>
<td>8 (38.1%)</td>
<td>10 (52.6%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Duration of illness (mean ± SD)</td>
<td>8.38 ± 0.4</td>
<td>8.41 ± 0.5</td>
<td>0.98</td>
</tr>
</tbody>
</table>

### Fig. 2

Bar diagram shows effect of aspirin on mortality, stroke and functional outcome at 3 months.

### Analysis of the effect of aspirin in patients having definite or highly probable TBM revealed significant reduction of death in the aspirin group. 7 out of 35 (20%) patients in the aspirin group died compared to 15 out of 36 (41.7%) patients in the placebo group ($P=0.05$). The frequency of stroke was also reduced in the aspirin (26.8%; 7 out of 26) compared to the placebo (43.4%; 10 out of 23) groups though insignificant ($P=0.22$).

### 4.3. Adverse effects

33 Patients had adverse events which included vomiting in 28, epigastric discomfort in 1, rashes in 4 and jaundice and altered liver function in 28 patients. The side effects were not different between the two groups. In 2 patients aspirin had to be temporarily withdrawn before shut surgery.

### 5. Discussion

In our study, aspirin resulted in 19.1% absolute risk reduction in ischemic stroke and 22% absolute risk reduction in mortality of TBM. The observed reduction in the frequency of stroke may be due to antplatelet and antithrombotic effects of aspirin. Vasculitis is a common complication of TBM. In an autopsy study, vasculitis was found in 41%; but organizing thrombus was uncommon. The vascular narrowing and the location of infarction however did not correlate. In other studies, organizing thrombus was reported in TBM patients [3,21]. There are several pathophysiological mechanisms responsible for brain ischemia and infarction in TBM. The basal exudates in TBM are located in interpeduncular fossa and extend anteriorly surrounding anterior cerebral artery; laterally along the Sylvian fissure surrounding the terminal part of internal carotid artery and middle cerebral artery with their penetrating branches. Caudally the exudate spreads to pontomesencephalic, cerebellar and medullary cisterns.
where vertebrobasilar and cerebellar arteries are located. The medium size vessels develop periarteritis, and later panarteritis whereas the penetrating small vessels develop endarteritis [2]. The medium size vessels develop periarteritis, and later panarteritis.

Aspirin although resulted in reduction in the frequency of stroke but did not achieve statistical significance, which may be due to the multiplicity of underlying pathophysiological mechanisms responsible for infarction in TBM. Corticosteroids have been reported to reduce thrombocytopenia and allergy. In the present study, however, the in vivo inhibitory effect on blood platelet aggregation was not statistically significant. In the aspirin group, more patients were lost from follow up compared to the placebo group. Tobacco intake however was not evaluated. In the aspirin group, patients with aspirin compared to 93% without, although both the treatment groups. In none of the patients, aspirin had to be withdrawn except in one patient with coronary artery disease who developed gastrointestinal bleeding.

The reduction in mortality in the aspirin group may be due to reduction in frequency or severity of stroke or both. Moreover the combination of aspirin and corticosteroid resulted in significant reduction of mortality compared to those who did not receive these treatments (P=0.047). These results however are based on small sample size and need confirmation in a larger study. The conventional stroke risk factors such as diabetes mellitus, hypertension and coronary artery disease were similar in the aspirin and the placebo groups. Tobacco intake however was not evaluated. In the aspirin group, more patients were lost from follow up compared to the placebo group, which was incidental. Our results therefore should be considered with these limitations. Presence of tuberculoma in our study was associated with improved survival which may suggest better immunity in these patients.

Aspirin results in gastrointestinal toxicity, gastric hemorrhage, thrombocytopenia and allergy. In the present study, however, the adverse reactions were similar in both the aspirin and the placebo groups. In the patients without aspirin, aspirin had to be withdrawn except in 2, in whom it was temporarily discontinued before the shunt surgery.

Aspirin has not been systematically evaluated for preventing stroke in other central nervous system vasculitides. In a retrospective review of 175 patients with giant cell arteritis, 36 patients received low dose aspirin for ischemic heart disease. Stroke occurred in 3% patients with aspirin compared to 93% without, although both the groups received corticosteroids [23]. In antiphospholipid antibody syndrome (APLA) syndrome, aspirin resulted in reduction of ischemic stroke. In a retrospective study on 103 consecutive patients on APLA syndrome, 37 had systemic lupus erythematosus (SLE). 4 out of 10 SLE patients without aspirin and 3 out of 27 with aspirin developed thrombosis [24]. Though TBM is associated with vasculitis in half the patients but its nature is different from the above mentioned vasculitides. The role of aspirin in TBM therefore needs further evaluation.

In the present study, only 37.3% patients received corticosteroids; it is based on relatively small sample size for subgroup analysis and there was high dropout in the aspirin group. In spite of these limitations, there are some indications that aspirin may be potentially beneficial in TBM in preventing stroke and mortality especially in combination with corticosteroids.

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References