

**Research Article**

**Assessment of effects of aspirin on mortality in cases of tuberculous meningitis stage-III having age 1-15 years**

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[Received: 30/04/2019; Accepted: 20/07/19; Published: 23/07/2019]

**ABSTRACT**

**Objectives:** To evaluate the effect of aspirin on mortality occurring within 2 months of starting treatment in tuberculous meningitis (TBM) stage III patients in patients 1-15 years of age.

**Material and methods:** This randomized controlled trial was conducted at Department of Pediatrics, Lahore General Hospital Lahore from January 2018 to June 2018. Total 162 patients of 1-15 years of age with TBM stage III were included. Patients were divided in Group A (Aspirin group having 81 patients) and Group B (Placebo group having 81 patients). Outcome was noted in terms of mortality in both groups.

**Results:** Out of a total of 162 children, there were 79 (48.8%) male and 83 (51.2%) female. Majority of the children, 106 (65.4%) were from 6 to 10 years of age. Miliary TB was found in 31 (19.1%) children. Presence of severe wasting was found amongst 40 (24.7%). Overall mortality was noted in 43 (26.5%) children. When both groups were divided, all the variables were found not to be statistically significant (p value > 0.05).

**Conclusion:** In children with TBM stage III, aspirin resulted in reduction in mortality but did not achieve statistical significance.

**INTRODUCTION:**

About 1/3<sup>rd</sup> individuals are infected with Mycobacterium tuberculosis globally; every year about 9 million individuals suffer from this disease and most of the TB cases reported in Asia, Africa and western Pacific. Annually 2 million individuals died due to TB and about 10% of whom are <15 years of age. About 98% of deaths occur in Africa and Asia<sup>1</sup>.

About 5.7 million individuals infected by TB in Pakistani population and about 260,000 cases occurred every year.<sup>2</sup> In Pakistani population, exact figure of children infected with TB is unknown.<sup>3</sup> Tuberculous meningitis (TBM) is the most severe manifestation of tuberculosis with high mortality and morbidity rate.<sup>4</sup> Pathological manifestations of TBM are exudates,

tuberculoma, hydrocephalus and stroke. Cerebro-vascular complications of TBM usually occur as bilateral or multiple lesions in the areas of middle cerebral artery.<sup>5</sup> Late diagnosis can lead to worst outcome of TBM.<sup>6</sup>

It was thought that morbidity and mortality can be reduced by combine use of corticosteroids and antitubercular treatment but it has no role in the reduction of stroke rate.

Further studies are required to prove the role of aspirin in reducing mortality and stroke rate in cases of TBM.<sup>7</sup>

One study is available with aspirin that showed reduction in stroke as compared to placebo (24.2% vs 43.3%) and mortality (21.7% vs 43.3%) in cases of TBM.<sup>8</sup>

I wanted to the role of aspirin in reducing mortality in TBM in children as the available study includes both children and adults as no study was conducted previously on aspirin in Pakistan. TBM is not uncommon in Pakistan so we should try to search new drugs to improve the outcome.

#### **RESEARCH METHODOLOGY:**

This randomized controlled trial was conducted at Department of Pediatrics, Lahore General Hospital Lahore from January 2018 to June 2018. Non probability consecutive sampling technique was used. All the patients of 1-15 years of age with TBM stage III were included. These criterias were confirmed by history, examination and investigations (Complete blood count (CBC) with platelets count, Prothrombin time (PT), Activated partial thromboplastin time (APTT), Bleeding time (BT), Liver function test (LFT's), renal function test (RFT's) and CT brain). Patients were excluded from the study who were on antitubercular treatment (by history), had bleeding diathesis (by history, examination and with platelets count, PT, APTT and BT), aspirin allergy (by history), liver disease (by history, examination and LFT's), kidney failure (by history, examination and RFT's) or subarachnoid hemorrhage (by examination and CT brain). The study was approved by the Institutional Ethical Committee. Children with TBM admitting in the ward through accident and emergency fulfilling the inclusion criteria were selected. Informed consent was taken from the parents / guardian. Randomization was done by lottery method into group A (aspirin) and B (placebo). Demographic data as well as brief history and examination was documented on Performa (annex A). All patients were treated with 4 antitubercular drug RHZE regimen (rifampicin 15mg/kg, isoniazid 10mg/kg, pyrazinamide 25mg/kg and ethambutol 15mg/kg) per oral daily for 2 months followed by RH (rifampicin 15mg/kg, isoniazid 10mg/kg) for 10 months<sup>9</sup> along with corticosteroid (prednisolone 1-2mg/kg) per oral daily for 4 weeks and tapered in next 4 weeks. Oral aspirin was given to only group A patient at 60mg/kg per day divided 12 hourly starting with

the first dose of antitubercular therapy. All the data was entered on a pre-designed Performa (annex A) for each patient.

Data was analyzed by using SPSS. Age was presented as mean and SD and outcome (mortality), gender were presented as frequencies and percentages. Effect modifiers were controlled by stratification of age (1-5 years, 6-10 years, and 11-15 years) sex, associated miliary tuberculosis (defined as millet like 1-5mm seeding of TB bacilli in the lung, as evident on chest x-ray), and patient with severe wasting (defined as a weight-for-length less than minus three SD). Chi square test was applied to compare the quantitative data (sex, mortality, presence of miliary TB, presence of severe wasting) and p value < 0.05 were taken as statistically significant.

#### **RESULTS**

Out of a total of 162 children, there were 79 (48.8%) male and 83 (51.2%) female. Mean age was 7.3 years with standard deviation of 3.07 years. Majority of the children, 106 (65.4%) were from 6 to 10 years of age while 37 (22.8%) 1 to 5 years and 19 (11.7%) 11 to 15 years of age. Miliary TB was found in 31 (19.1%) children. Presence of severe wasting was found amongst 40 (24.7%). Overall mortality was noted in 43 (26.5%) children. (Figure No.1)

When both groups were divided, there were 18 (22.2%) children from 1 to 5 years in Group A whereas 19 (23.6%) in Group B, 53 (65.4%) from 6 to 10 years in Group A and same in Group B, while 10 (12.3%) from 11 to 15 years and 9 (11.1%) in Group B. After applying chi square, no statistical significance (p value = 0.961) was found between the both groups (Table No.1)

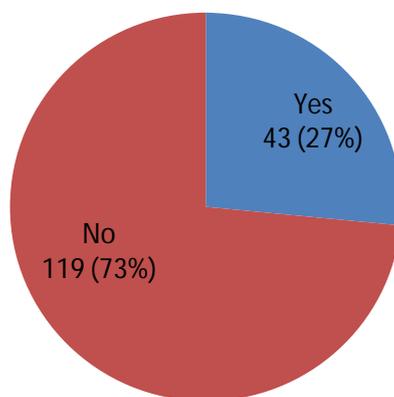
There were 37 (45.7%) male in Group A and 42 (51.9%) in Group B whereas 44 (54.3%) female in Group A and 39 (48.1%) in Group B. No statistical significance (p value = 0.432) was found between both the groups. (Table No.2)

As far as presence of miliary TB between the both groups is concerned, it was found 17 (21.0%) in Group A and 14 (17.3%) in Group B with an insignificant p value of 0.549. (Table No.3)

Presence of severe wasting was found in 18 (22.2%) children in Group A and 22 (27.2%) in Group B with an insignificant p value of 0.466. (Table No.3)

There were 18 (22.2%) children who died in Group while 25 (30.9%) in Group B. No statistical significance for mortality between the both groups was found as p value turned out to be 0.213. (Table No.3)

**Figure No.1:** Overall Mortality



**Table No.1:** Comparison of age between both the groups

Age (Years)	Groups		Total	P value
	A	B		
1-5	18 (22.2%)	19 (23.6%)	37 (22.8%)	0.961
6-10	53 (65.4%)	53 (65.4%)	106 (36.6%)	
11-15	10 (12.3%)	9 (11.1%)	19 (11.7%)	
<b>Total</b>	81 (50%)	81 (50%)	162 (100%)	

**Table No.2:** Distribution of Gender between both the groups

Gender	Groups		Total	P value
	A	B		
Male	37 (45.7%)	42 (51.9%)	79 (48.8%)	0.432
Female	44 (54.3%)	39 (48.1%)	83 (51.2%)	
<b>Total</b>	81	81	162	

**Table No.3:** Comparison of miliary TB, presence of severe wasting and mortality between both the groups

	Group A	Group B	P value
<b>Miliary TB</b>	<b>17 (21.0%)</b>	<b>14 (17.3%)</b>	<b>0.549</b>
<b>Presence of Severe Wasting</b>	<b>18 (22.2%)</b>	<b>22 (27.2%)</b>	<b>0.466</b>
<b>Mortality</b>	<b>18 (22.2%)</b>	<b>25 (30.9%)</b>	<b>0.213</b>

**DISCUSSION:**

The objective of present study was assess the effect of aspirin on mortality occurring within 2 months of starting treatment in tuberculous meningitis (TBM) stage III patients in patients 1-15 years of age. In current study, miliary TB was found in 17 (21.0%) children in Group A and 14 (17.3%) in Group B. Miliary TB could be an indicator for TBM in the countries with high prevalence of TB.<sup>10</sup> Concomitant miliary tuberculosis should bring TBM to mind in cases with an unknown origin. Female predominance, longer symptom duration, higher protein level in

CSF may be remarkable in patients with TBM accompanied with miliary TB.<sup>11,12</sup>

Not many studies have evaluated the impact of aspirin on outcome of patients with TBM. In the present study, mortality was reduced in children who received aspirin (22.2%) as compared to those who were given placebo (30.9%). Although, there was reduction in terms of mortality in children who used aspirin but these results were not statistically significant (p value = 0.213). Possible role of aspirin in the cases of TMB was reported in 2 studies. In first study aspirin compared with placebo.<sup>8</sup> In this study

aspirin showed statistically insignificant reduction in stroke rate after 3 months and significant reduction in mortality rate.

The second study was with 3 parallel arms (low- and high-dose aspirin and placebo).<sup>13,14</sup>

This study showed no impact on mortality and morbidity. Outcomes in the high-dose aspirin group compared favourably with the other treatment groups despite younger age and more severe neurological involvement.<sup>15</sup> Aspirin has also been found to be associated with 19.1% absolute risk reduction in ischemic stroke and 22% absolute risk reduction in mortality of TBM.<sup>8</sup> The observed reduction in the frequency of stroke may be due to antiplatelet and antithrombotic effects of aspirin.<sup>16</sup>

### CONCLUSION:

In children with TBM stage III, aspirin resulted in reduction in mortality but did not achieve statistical significance. Further studies with large sample size could ensure better understanding and outcome for the role of aspirin in children with TBM.

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