Original Article

The Effect of Aspirin on Mortality in Tuberculous Meningitis

Effect of Aspirin on TB Meningitis

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ABSTRACT

Objective: 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.

Study design: A randomized open label placebo controlled trial

Place and Duration of study: The study was conducted at Pediatric unit II B.V.H. from March 2015 to September 2015.

Materials and Methods: A total of 162 patients of 1-15 years of age with TBM stage III were included in the study. 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. 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 10months along with corticosteroid (predisolone 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.

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 variable 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 statistically significance

Key Words: Aspirin, Mortality, Tuberculous Meningitis

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INTRODUCTION

Tuberculosis (TB) is a global health issue. One third of the world population is infected with Mycobacterium tuberculosis; each year 9 million people develop disease and about 95% of the world's cases of TB occur in South East Asia, sub-Saharan Africa and Western Pacific. TB is the second leading killer after human immunodeficiency virus with annually about 2 million deaths; 10% of whom are younger than 15 years old. About 98% of those deaths occur in the developing countries of Asia and Africa[1]. In Pakistan approximately 5.7 million people suffer from TB, with 260,000 new cases occurring every year [2]. The exact population of children with TB in Pakistan is unknown[3]. Tuberculous meningitis (TBM) is the most severe manifestation of tuberculosis in term of high mortality and morbidity[4].

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Pathological manifestations of TBM are exudates, tuberculoma, hydrocephalus and stroke. Cerebrovascular complications of TBM that typically occur as multiple or bilateral lesions in the territories of middle cerebral artery perforating vessels are termed as tuberculous vasculopathy[5]. Vessel pathology appears to be a consequence of its immersion in the local inflammatory exudates leading to luminal thrombosis. There is some evidence that vasospasm may mediate stroke early in the course of disease and proliferative intimal disease in later strokes.

The worst outcome of TBM is mainly due to the delay in diagnosis and mostly patient present at stage III[6]. Corticosteroids with antitubercular therapy were thought to reduce mortality and morbidity but their role in reducing strokes has not been proven. Aspirin also reduces mortality and its role in reducing stroke in TBM needs further studies [7]. One study is available with aspirin that showed reduction in stroke 24.2% compared to placebo group 43.3% and mortality 21.7% compared to placebo group 43.3% [8].

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.

MATERIALS AND METHODS

This was a randomized controlled study, conducted in Pediatric unit II B.V.H. Bahawalpur from March 2015 to September 2015. 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 10months[9] along with corticosteroid (predisolone 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.

The collected data was analyzed by SPSS version 10. Mean and standard deviation were calculated for quantitative variables like age. Frequency and percentage were calculated for qualitative variables like outcome (mortality). Effect modifiers were controlled by stratification of age (1-5years, 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)

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%)	
Total	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%)	
Total	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
Miliary TB	17 (21.0%)	14 (17.3%)	0.549
Presence of Severe Wasting	18 (22.2%)	22 (27.2%)	0.466
Mortality	18 (22.2%)	25 (30.9%)	0.213

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)

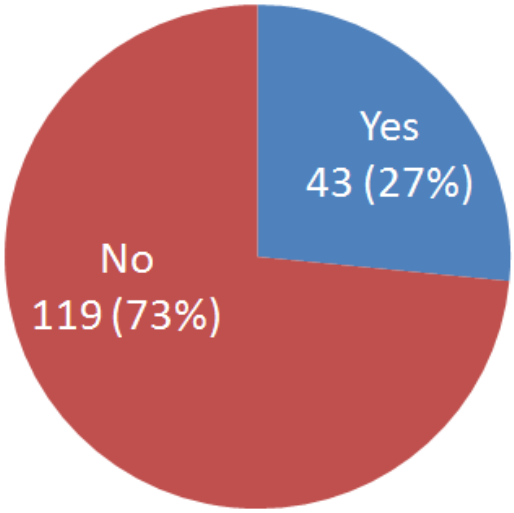

Figure No.1: Overall Mortality

DISCUSSION

The recommended first-line treatment agents for all forms of CNS tuberculosis are Isoniazid, Rifampicin, Pyrazinamide and Ethambutol taken daily either individually or in combination form.[10] Patients are usually treated for a minimum of 10 months. Therapy is extended to at least 12 months in those who fail to respond, or if treatment interruptions have occurred for any reason. Isoniazid penetrates the CSF freely and has potent early bactericidal activity. At standard doses isoniazid achieves CSF levels 10-15 times the minimum inhibitory concentration of *M. tuberculosis*.[11,12]

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.[13] 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.[14,15]

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).

Two recent studies have examined the possible benefits of aspirin in TBM treatment. The first study was a randomized controlled trial of aspirin versus placebo in 118 Indian adults.[8] Aspirin was associated with a non-significant reduction in stroke at 3 months, and a significant reduction in mortality (21.7 versus 43.4%, P = 0.02). The effects of aspirin are difficult to interpret, however, as prednisolone was also given to some patients such as those with severe disease at baseline, or those whose clinical condition worsened during treatment. The second study was a randomized controlled trial with three parallel arms (low- and high-dose aspirin and placebo) in South African children.[16,17] Aspirin had no impact on morbidity (hemiparesis and developmental outcome) or mortality. Aspirin was well tolerated, but one death occurred and was probably related to aspirin. Outcomes in the high-dose aspirin group compared favourably with the other treatment groups despite younger age and more severe neurological involvement.[18] 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.[8] The observed reduction in the frequency of stroke may be due to antiplatelet and antithrombotic effects of aspirin.[19,20]

CONCLUSION

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

Conflict of Interest: The study has no conflict of interest to declare by any author.

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