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A STUDY TO DETERMINE WHETHER HOW MUCH EFFECTIVE USING ASPIRIN PROVES IN TERMS OF MORTALITY REDUCTION WHILE TREATING TUBERCULOUS MENINGITIS

[1]Dr. Sana Zafar, [2]Dr. Sidra Rafiq, [2]Dr. Aleema Hasan

[1]Sir Gangaram Hospital, Lahore, [2]Sheikh Zayed Hospital, Lahore.

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Abstract:

Objectives: *The research objective is the evaluation of aspirin effect on the occurrence of mortality within two months of TBM (Tuberculous Meningitis) stage-III treatment among (1 to 15) years age patients.*

Materials & Methods: *The research method is a randomised open-label placebo-controlled trial, carried out at Mayo Hospital, Lahore from February to September 2017. We selected 162 (1 – 15) years' patients with stage-III TBM. We divided patients between Group – A (Aspirin) and Group – B (Placebo) consisting 81 patients each. We recorded mortality as an outcome for both groups. We treated each patient with 04 anti-tubercular drugs; RHZE regimen (per-oral for two months daily) including Isoniazid (10 mg/kg), Rifampicin (15 mg/kg), Ethambutol (15 mg/kg), and Pyrazinamide (25 mg/kg), then RH (for ten months) including Isoniazid (10 mg/kg) and Rifampicin (15 mg/kg) with Corticosteroid (for one month) including Prednisolone (1 – 2 mg/kg) and tapered in four coming weeks. However, Group – A patient only received (60 mg/kg)/day of oral aspirin divided 12-hourly with the start of anti-tubercular therapy 1st dose.*

Results: *The number of male and female patients was 48.80% (79) and 51.20% (83) respectively. Out of 162 patients, 65.40% (106) were having (6 – 10) year's age. We found Miliary and severe wasting among 19.10% (31) and 24.70% (40) patients respectively. We noted a 26.50% (43) mortality among patient children. After we divided groups, we found variables statistically not significant having P-value > 0.050.*

Conclusion: *Aspirin proves to be reducing mortality among TBM (stage-III) children with no statistical significance achieved.*

Keywords: *Tuberculous Meningitis (TBM), Tuberculosis (TB), Miliary Tuberculosis (MTB) and Aspirin.*

Corresponding author:

Dr. Sana Zafar,

Sir Gangaram Hospital, Lahore.

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INTRODUCTION:

Tuberculosis is a worldwide health problem infecting 1/3 population globally. Nine million people develop this disease, Western Pacific, Asia, and sub-Saharan Africa consist of 95% of world's TB cases. TB holds the second position being mortal after immune-deficiency virus among human, killing 2 million annually, 10% of which are less than fifteen years old. Developing countries like Africa and Asia have 98% of death occurrence [1]. Pakistan consists 5.70 million (approx.) TB cases with 260,000 cases occurring new each year [2]. However, an exact number of cases is unknown in Pakistan [3]. TBM is the most severe form of TB in terms of morbidity/mortality [4]. Tuberculoma, stroke, hydrocephalus, and exudates are pathological manifestations of TB meningitis. Tuberculous vasculopathy is a term means, Cerebro-vascular complications which occur as bilateral/multiple lesions in the middle cerebral artery territories, perforating vessels [5]. It appears that immersion in the local-inflammatory-exudates that leads to luminal-thrombosis causes vessel pathology. Some evidence shows vasospasm may cause stroke in the early stage of the disease while in later strokes, may cause proliferative intimal disease. Delayed diagnosis is the worst outcome of TBM where the patient is present at Stage-III [6]. According to the study, mortality and morbidity reduce with corticosteroids along with anti-tubercular therapy but there is no proof for stroke reduction. Aspirin has the same outcomes with stroke reduction proof requiring more study [7]. A study shows stroke reduction and mortality rate by aspirin and placebo to be 24.20% and 43.30% for stroke and 21.70% and 43.30% for mortality respectively [8]. The purpose of this research was to determine the role of aspirin in reducing mortality due to TBM among children and adults, as there was no study available about the said purpose in Pakistan. As TBM is a common disease in Pakistan, therefore, the need for an effective drug is necessary to achieve improved outcomes.

MATERIAL AND METHODS:

The research method is randomised open-label placebo-controlled trial, carried out at Mayo Hospital, Lahore from February to September 2017. We used the technique of Non-Probability Consecutive-sampling. Inclusion criteria were (1 to 15) years' age patients having stage-III TMB. Examination, investigation, and history (Prothrombin time, complete blood, and platelets count, brain CT, Liver/Renal function test, activated partial thromboplastin time, and bleeding time) supported this criterion. We excluded patients having a history of anti-tubercular treatment, Prothrombin time, complete blood, and platelets count, brain CT, Liver/Renal function test, Activated partial thromboplastin time, bleeding time, liver disease, aspirin allergy, and kidney failure. We selected children with TBM fulfilling the inclusion criteria after taking approval from the Institutional Ethical Committee and informed consent from parents/guardian of the patients. We used the lottery method for group division into A (aspirin) and B (placebo). We used a Performa to record demographic data, examination, and history of patients. We treated each patient with 04 anti-tubercular drugs; RHZE regimen (per-oral for two months daily) including Isoniazid (10 mg/kg), Rifampicin (15 mg/kg), Ethambutol (15 mg/kg), and Pyrazinamide (25 mg/kg), then RH (for ten months) including Isoniazid (10 mg/kg) and Rifampicin (15 mg/kg) with Corticosteroid (for one month) including Prednisolone (1 – 2 mg/kg) and tapered in four coming weeks. However, Group-A patients only received (60 mg/kg)/day of oral aspirin divided 12-hourly with the start of anti-tubercular therapy 1st dose. We entered all data of each patient on Annex-A (predesigned Pro-forma) and analyzed it through SPSS. We presented age as Mean and Standard Deviation and used percentage and frequency to present mortality (outcome) and gender. We used stratification of age, sex, severe wasting (Weight for length > -3 SD), and associated MTB (1 to 5 mm millet like seeding of TB bacilli present in lungs which is evident through chest X-ray) to control effect modifiers. To compare quantitative data (Mortality, sex, and presence of severe wasting and MTB), we used the Chi-Square test and took statistically significant P-value as < 0.05.

RESULTS:

The number of male and female patients, out of 162, was 48.80% (79) and 51.20% (83) respectively. Out of 162 patients, 65.40% (106), 22.80% (37), and 11.70% (19) were having (6 – 10), (1 – 5), and (11 – 15) year's age respectively with 7.30 and ±3.07 as mean age and SD respectively. We found 19.10% (31), 24.70% (40), and 26.50% (43) children with MTB, severe wasting and mortality respectively. We noted 22.20% (18) and 23.60% (19) children from Group – A and Group – B in (1 – 5) years' age group respectively, while 65.40% (53) were from (6 – 10 years' age group both Group – A and Group – B each, whereas 12.30% (10), and 11.10% (9) children from (11 – 15) years' age group in Group – A and Group – B respectively. We found no statistically significant P-value (0.961) between these groups after applying the Chi-square test. The number of male and female patients in Group – A was 45.70% (37) and 54.30% (44) respectively; whereas, in Group – B was 51.90% (42) and 48.10% (39) respectively. There was no statistically significant P-

value (0.432) between both groups. Presence of MTB in Group – A and Group – B was 21% (17) and 17.30% (14) respectively with P-value (0.549) as insignificant. Presence of severe wasting in Group – A and Group – B was 22.20% (18) and 27.20% (22) respectively with P-value (0. 466) as insignificant. We noted mortality in Group – A and Group – B to be 22.20% (18) and 30.90% (25) respectively with P-value (0. 213) as insignificant.

Table – I: Overall Mortality

Mortality	Number	Percentage
Yes	43	27
No	119	73

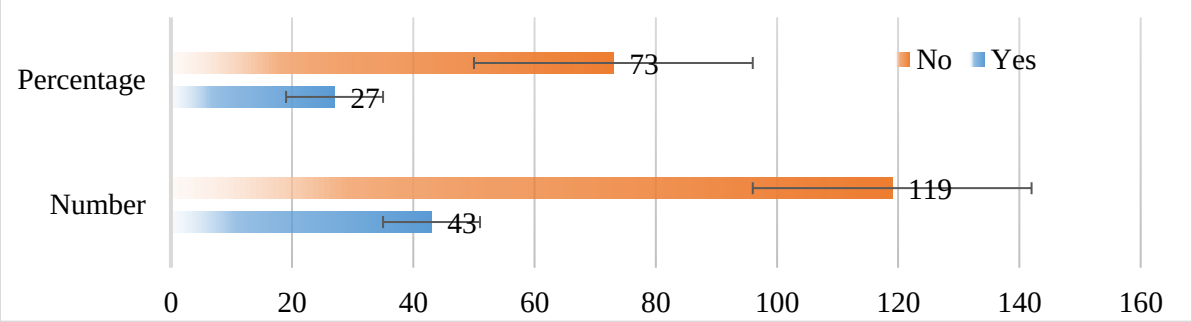


Table – II: Age and Gender Stratification

Age and Gender		Group – A		Group – B		Total		P-Value
		No	%	No	%	No	%	
Age	1 to 5 Years	18	22.2	19	23.6	37	22.8	0.961
	6 to 10 Years	53	65.4	53	65.4	106	36.6	
	11 to 15 Years	10	12.3	9	11.1	19	11.7	
Gender	Male	37	45.7	42	51.9	79	48.8	0.432
	Female	44	54.3	39	48.1	83	51.2	

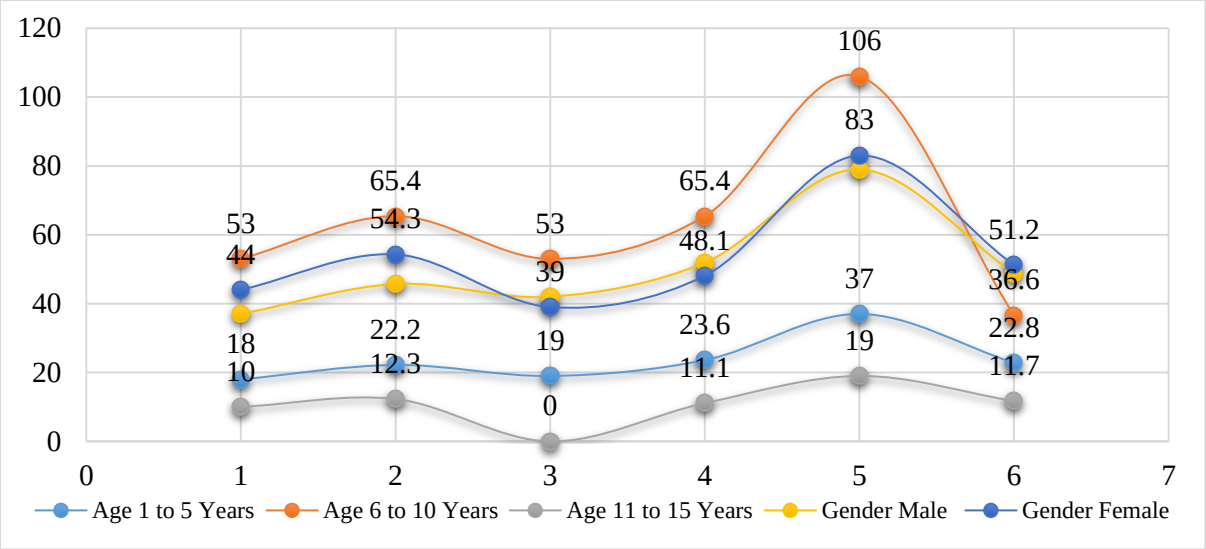
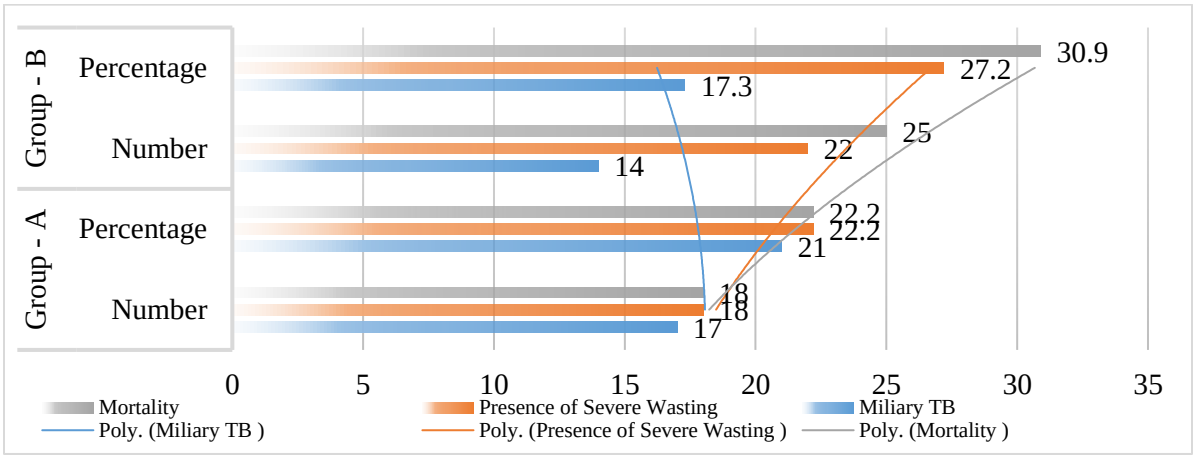


Table – III: Miliary TB, Mortality and Severe Wasting Prevalence

Variables	Group – A		Group – B		P-Value
	Number	Percentage	Number	Percentage	
Miliary TB	17	21	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



DISCUSSION:

The research objective was the evaluation of aspirin effect on the occurrence of mortality within two months of TBM (stage-III) treatment among (1 to 15) years age patients. In our study, we found MTB among 21% (17) and 17.30% (14) patients of Group – A and Group – B respectively. MTB can be a sign for TBM among counties having TB with high prevalence [10]. Concomitant MTB should lead thoughts to TBM where the origin of cases is unknown. A lengthy symptom duration, CSF with higher protein-level and female predominance may be found among TBM patients having MTB [11, 12]. There are no studies evaluating aspirin impact on the outcome of TBM patients. Our study shows reduced mortality (22.20%) with aspirin comparing to placebo (30.90%). Even though aspirin reduced the mortality rate but the outcome is still not statistically significant (P-value equals to 0.213). Two studies show possible effects on aspirin in TMB. In the 1st study (Aspirin-Placebo

comparison), aspiring showed stroke-rate reduction statistically insignificant after three months, however, reduction of mortality-rate was significant [8]. The 2nd study having placebo with aspiring dose as low and high [13, 14]. The study did not find any impact on morbidity and mortality. The outcome of aspirin-group with high-dose produced favourable results comparing to the other groups (despite severe neurological involvement and younger age) [15]. The study also found an aspiring association of 19.10% and 22% with absolute risk-reduction in ischemic-stroke and mortality of TBM respectively [8]. The possibility of reduced stroke frequency may be due to aspirin's anti-thrombotic and antiplatelet effects [16].

CONCLUSION:

The study concludes that aspirin reduces mortality among stage-III TBM children with no statistical significance. Furthermore, a large sample-size of TBM children may increase the understanding of the role of aspirin among TBM patients.

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