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Research Paper

# Efficacy and safety of aspirin as an adjunctive therapy in tubercular meningitis: A systematic review and meta-analysis

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ABSTRACT

*Background:* Tubercular meningitis (TBM) is associated with high mortality and stroke with chronic neurological sequelae even with best of care and antitubercular therapy. Studies have shown that aspirin as an adjunctive therapy might play some role in management of TBM. This systematic review and meta-analysis has been planned to evaluate the efficacy and safety of aspirin as an adjunctive therapy in TBM patients.
*Methods:* We conducted a systematic search of randomized controlled trials in patients with tubercular meningitis published till October 2019 in all major clinical journals. Study was registered with PROSPERO with registration number: CRD42019136689. Articles were tested for eligibility and assessed for quality and various bias. Data synthesis and analysis was done using Review manager 5.3. The primary end point for assessment of efficacy was mortality at three months. The secondary end point was stroke or composite outcome of stroke and mortality at three months. Adverse effects were also assessed as secondary safety end point.
*Findings:* Overall, three eligible randomized controlled trials with 365 participants were included that provided quantitative data for this meta-analysis. The analysis of primary and secondary end points was done using fixed effect model. There was not significant reduction in mortality [hazard ratio 0.78 (95% CI 0.45−1.35, $p$ = 0.37)] and composite outcome of mortality and new onset stroke [hazard ratio 0.86 (95% CI 0.60−1.24, $p$ = 0.43)] in aspirin group as compared to placebo. However, aspirin as compared to placebo significantly reduced new onset stroke [hazard ratio of 0.51 (95% CI 0.29−0.87, $p$ = 0.01)].
*Interpretation:* We did not find significant reduction in mortality and composite outcome (mortality and new onset stroke) with aspirin as compared to placebo but there was significant reduction in new onset stroke in aspirin group as compared to placebo with Number Needed to Treat (NNT) = 10, which might be of clinical importance since stroke is responsible for high mortality and morbidity in these subset of patients. However, a large well conducted randomized controlled trial is required to put more light on the available evidence.


## 1. Introduction

According to the World Health Organization (WHO) September 2018 report, tuberculosis (TB) is one of the top 10 causes of death worldwide and a leading killer of patients who are HIV positive [1]. TB is a global epidemic with 10 million people diagnosed with tuberculosis and 1.5 million died from the disease as per 2018 WHO report. Tubercular meningitis (TBM) an important neuro-infectious condition which leads to high mortality and morbidity with chronic neurological sequelae. One factor with is responsible for high morbidity and mortality in these patients is stroke [3]. Mortality is three times higher in TBM with infarction as compared to without. This could be explained by a hypothesis that TBM is a hypercoagulable state (decrease in protein S, increase in factor VIII leads to prothrombotic state) which could be the reason for ischaemic stroke and neuropathy in these patients [2]. Stroke occurs in around 15 to 57% of TBM patients especially in severe cases and with advanced stage [3]. Of them around 20% of patients have focal neurological deficits [3]. Current recommended therapy in these patients is anti-tubercular therapy along with corticosteroids and supportive care [4]. However, even with best of care the prognosis in these patients is bad with neurological sequelae and high mortality.

Since TBM is a hypercoagulable state, aspirin might play some role as an adjunctive therapy in management of these patients. An open label phase-II trial showed aspirin (150 mg daily) resulted in absolute risk reduction of 19.1% in stroke and significant reduction in mortality (21.7%) compared to placebo group (43.4%) at 3 months [5]. A recent randomized controlled trial

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**Research in context**

*Evidence before this study*

Since, TBM (Tubercular meningitis) is a hypercoagulable state, so aspirin as an adjuvant therapy has been tried for management of these patients. We under-took this systematic review and meta-analysis to look into evidence available for usefulness of aspirin as adjuvant therapy in TBM over standard of care.

All randomised controlled trials published till October 2019 were included in the study. The conduct, design and reporting of results were in accordance to PRISMA guidelines. We found four relevant trials, of which three trials were included in the meta-analysis.

*Added value of this study*

Although addition of aspirin as adjuvant treatment over standard of care did not show significant reduction in mortality and composite outcome (mortality and new onset stroke), however there was significant reduction in new onset stroke with aspirin as compared to placebo [hazard ratio of 0.51 (95% CI 0.29−0.87, $p = 0.01$)].

*Implications of all the available evidence*

Since one of the main complications of TBM is cerebral stroke (reported incidence 13−57%), which leads to poor clinical outcome, this reduction could be clinically significant in reducing neurological sequelae and disability.

found that aspirin led to dose dependent inhibition of thromboxane (TxA2) and up regulation of pro-resolving CSF proteins [6]. They also found that aspirin lead to greater reduction in new infarcts and mortality by day 60 as compared to placebo and the reduction was higher in high dose aspirin (1000 mg) than low dose aspirin (81 mg) [34.4% events in placebo versus 14.8% in low dose aspirin 81 mg versus 10.7% in high dose aspirin 1000 mg]; although the difference did not reach statistical significance [6]. Rizvi et al [7] conducted a meta-analysis which showed that aspirin reduces the risk of new infarctions in patients with tubercular meningitis but do not reduce mortality. But this meta-analysis had some limitations. Firstly, they did not include new onset stroke as an outcome although they did include mortality. Secondly, they included an open label study in children [8] which enrolled only patients with severe TBM (stage III) with unconfirmed diagnosis.

Thus, we undertook this systematic review and meta-analysis to look into the evidence for the usefulness of aspirin in tubercular meningitis.

The primary objective of this meta-analysis was to determine whether addition of aspirin over and above anti-tubercular treatment is able to reduce mortality in patients with tubercular meningitis as compared with placebo. The secondary objective was to assess effect of aspirin on new onset stroke (brain infarction) and safety of aspirin in patients with tubercular meningitis.

## 2. Methods

### 2.1. Protocol and registration

The method of this systemic review and meta-analysis was described in an outline protocol that was registered with PROSPERO (International Prospective Register of Systemic Reviews) registration number: CRD42019136689.

### 2.2. Ethical approval

This study involved retrieval and synthesis of data from already published studies so ethical approval from Institutional Ethics Committee (IEC) for this meta-analysis was not required.

### 2.3. Selection of studies and participants

All randomized controlled trials, both open label and double blinded, published till October 2019 were included in the meta-analysis. The conduct, design and reporting of results are in accordance to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.

### 2.4. Eligibility criteria

Randomized controlled trials involving children or adult patients diagnosed with tubercular meningitis treated with anti-tubercular therapy, aspirin (either low dose or high dose) and/or corticosteroids were included in meta-analysis.

### 2.5. Exclusion criteria

Studies involving any of these were excluded from meta-analysis

1. HIV co-infected patients
2. Retrospective studies
3. Registries
4. Case control and cohort studies

### 2.6. Data sources and search strategy

Search was done by using key words or Medical Subject Headings (MeSH) terms and was combined using Boolean logic operators: 'AND', 'OR' and 'NOT' appropriately. Two independent reviewers (RR, SM) searched the following databases to ensure comprehensive search: Pubmed, Cochrane library, Embase, Google Scholar, Ovid and Scopus. The search terms were as follows; "tubercular meningitis" AND "Aspirin" OR "Anti-platelet" OR "Anti-inflammatory". No language restrictions were imposed. Relevant articles were selected according to eligibility criteria and ineligible studies were excluded. The full texts of selected articles were retrieved and reviewed by two independent reviewers (RR, SM) to ascertain the eligibility or suitability prior to data extraction. The reference list of the selected articles was hand searched so as to include studies which were missed by search strategy.

We found four relevant studies. Out of which three studies were included in meta-analysis and one study was excluded as it was a retrospective analysis of registry.

### 2.7. Data extraction and quality assurance

Data extraction was done by two independent reviewers (RR, SM). The following data was extracted from selected randomized controlled trials (RCTs): randomization, allocation concealment, blinding of study participants and personnel, blinding of outcome assessor, dose and duration of aspirin given with or without corticosteroid, missing data, primary efficacy outcome and safety outcome of the study. Extracted data was then entered in excel sheet maintaining data quality and was analyzed for primary and secondary outcome using Review manager 5.3.

### 2.8. Risk of bias assessment for individual studies

The following variables were assessed for risk of bias: sequence generation (selection bias), allocation concealment (selection bias),

blinding of participants, personnel (performance bias), blinding of outcome assessors (detection bias), completeness of outcome data (attrition bias) and evidence of selective outcome reporting (reporting bias) for individual studies. Study quality was assessed independently by two reviewers (RR, SM) and any discrepancies were resolved by consensus.

### 2.9. End points

The primary end point for assessment of efficacy was mortality at three months.

The secondary end point was new onset stroke or composite outcome of stroke and mortality at three months. Adverse effects were also assessed as secondary safety end point.

### 2.10. Data synthesis and analysis

Eligible studies were presented in form of evidence table. Analysis was done using Review manager 5.3. Three studies Mai et al. [6], Misra et al. [5] and Schoeman et al. [9] were included for primary analysis and secondary analysis. Schoeman et al. was different from other two studies in terms of younger age of patients and aspirin was given for only one month so for sensitivity analysis only two studies; Mai et al. [6] and Misra et al. [5] were assessed.

### 2.11. Heterogeneity testing

Heterogeneity between the results was assessed using Cochran's *Q* test and quantified with *I*-square statistic. Probability (*p*-value) $< 0.1$ was considered as statistically significant heterogeneity.

### 2.12. Role of funding source

No grant or funding was taken for this study.

## 3. Results

### 3.1. Study selection

During search limit period, a total of 17 relevant original articles were selected using MeSH terms mentioned above. Study selection process is described in Fig. 1. After excluding duplicates, six unique articles were selected. Three more articles were excluded because one was a review article, one was an observational study and third was a poor quality open label RCT. The RCT did not include all stages of TBM and did not include new onset stroke as an outcome so was excluded from main analysis. However, sensitivity analysis was performed with inclusion of this study. Finally, three randomized controlled trials were included in the meta-analysis.

### 3.2. Study characteristics

Overall, 365 participants were included in three trials that provided quantitative data for this meta-analysis (for individual study details, see Table 1). Largely primary efficacy outcome in these trials was death or new MRI proven brain infarction or stroke.

Misra et al. [5] included 118 adult patients with tubercular meningitis randomized into aspirin 150 mg daily or placebo. All patients received antitubercular therapy with or without corticosteroid. The primary outcome in this study was MRI (Magnetic resonance imaging) proven stroke at 3 months and secondary outcome were mortality and functional outcome at 3 months. This study found reduction in stroke in aspirin as compared to placebo but the difference was not statistically significant (22.5% vs 55%, $p = 0.08$). However, significant reduction in mortality was seen in aspirin group as compared to placebo (27.1% vs 43.4%, $p = 0.02$). Also aspirin was well tolerated and not withdrawn in any patient because of side- effects.

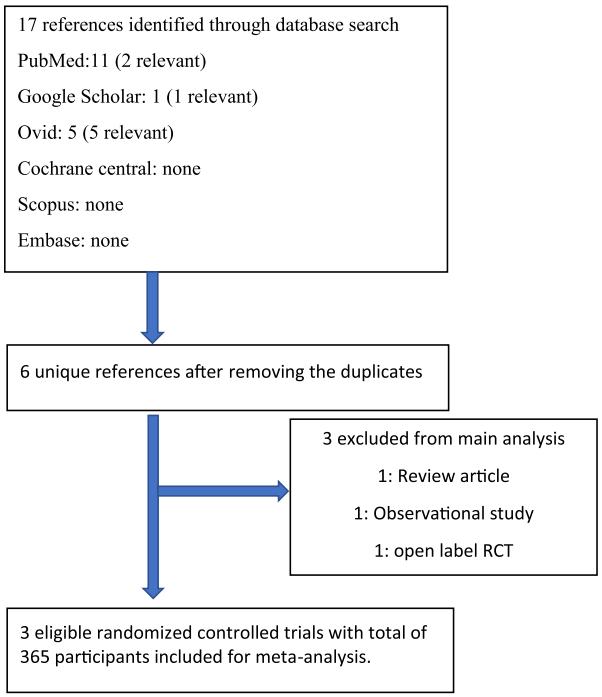


**Fig. 1.** PRISMA diagram of study selection.

Mai et al. [6] conducted a randomized double blind placebo controlled trial in 120 adult patients with tubercular meningitis comparing aspirin (low dose, high dose) with placebo added to first 60 days of antitubercular therapy and corticosteroid (dexamethasone). The primary efficacy endpoint in this study was new brain infarction confirmed by MRI or death by 60 days. The primary outcome occurred in 28.9% who were given placebo, 22.2% given low dose aspirin (81 mg) and 15.8% patients given high dose aspirin (1000 mg) with $p = 0.40$.

Schoeman et al. [9] conducted a randomized double blind placebo controlled trial comparing aspirin (low dose and high dose) with placebo in 146 children with tubercular meningitis. Aspirin irrespective of high or low dose did not show any significant benefit regarding morbidity (hemiparesis and developmental outcome) and mortality. However, this study gave aspirin and prednisolone for only one month and included only children with age ranging from 12 to 54 months.

### 3.3. Synthesis of results

All three studies including 365 patients were included for analysis of primary outcome using fixed effect model. The effect of aspirin compared to placebo on mortality was not significantly different [hazard ratio 0.78 (95% CI 0.45−1.35, $p = 0.37$)]. The test for heterogeneity, $I^2$ in our meta-analysis was 2%, indicating that there was minimal heterogeneity or inconsistency in the studies included (Fig. 2).

Secondary outcome: Aspirin as compared to placebo significantly reduced new onset stroke [hazard ratio of 0.51 (95% CI 0.29−0.87, $p = 0.01$)]. The test for heterogeneity, $I^2$ in our meta-analysis was 0%, indicating that there was no or minimal heterogeneity or inconsistency in the studies included (Fig. 3).

The effect of aspirin was also compared to placebo on composite of both outcomes (new onset stroke and mortality). There was no significant difference between the groups with hazard ratio of 0.86 (95% CI 0.60−1.24, $p = 0.43$). The test for heterogeneity, $I^2$ was 0%, indicating that there was no or minimal heterogeneity or inconsistency in the studies included (Fig. 4).

**Table 1**
Characteristics of involved studies.

| S.NO | Author name | Type of trial | Inclusion criteria | Sample size: Placebo | Intervention | Primary efficacy outcome | Secondary outcome | Results | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Misra et al. [5] | RCT (4 arms: Aspirin alone, CS alone, Aspirin + CS, placebo only) | Patients with TBM diagnosed on basis of clinical, CSF and radiological criteria | Placebo: 59<br>Aspirin: 59 | Aspirin 150 mg | Stroke on MRI at 3 months | Death, functional outcome and adverse outcomes at 3 months | Death: Aspirin only 8/24 (33.3%); Steroid only 8/17 (47.1%); Steroid + aspirin 3/23 (13%); Placebo only 14/35 (40%)<br>Stroke: Aspirin only 4/15 (26.2%); Steroid only 2/10 (20%); Steroid + aspirin 4/18 (22.2%); Placebo only 11/20 (55%) | Patients with both aspirin and corticosteroid had lower frequency of stroke (22.2%) vs without (55%, $p = 0.08$) but in isolation aspirin ($p = 0.18$) or CS ($p = 0.15$) did not significantly reduce stroke. |
| 2 | Mai et al. [6] | RCT (3 arms: Placebo, low dose and high dose aspirin) | Adults (>18 yrs) with suspected TBM (atleast 5 days of symptoms and CSF abnormalities) and negative HIV test | Placebo: 41<br>Low dose aspirin: 39<br>High dose aspirin: 40 | Low dose aspirin 81 mg; High dose aspirin 1000mg | Stroke on MRI or death by 60 days | Stroke, Death at 240 days (8 months) | Stroke or death: Placebo 11/38 (28.9%); Low dose 8/36 (22.2%); high dose 6/38 (15.8%)<br>Stroke: Placebo 8/35 (22.9%); Low dose 2/30 (6.7%); high dose 5/37 (13.5%)<br>Death: Placebo 4/41 (9.8%), low dose 6/39 (15.4%); high dose 1/40 (2.5%) | Subgroup analysis suggested potential reduction in new infarcts and deaths by day 60 in aspirin treated participants with microbiologically confirmed TBM |
| 3 | Schoeman et al. [9] | RCT (3 arms: Placebo, low dose and high dose aspirin) | Children with diagnosis of probable TBM on basis of clinical and CSF criteria | Placebo: 50<br>Low dose aspirin: 47<br>High dose aspirin: 49 | Low dose aspirin 75 mg; High dose aspirin 100 mg/kg/ day | Death, New onset hemiplegia at 6 months | Not mentioned | Death: Placebo: 1/50: Aspirin: low 2 + high 3 (5/96)<br>New hemiplegia: Placebo 2/50; Aspirin: (4 + 0) (4/96) | Aspirin irrespective of dose did not show any significant benefit regarding morbidity (hemiparesis) and mortality |

CSF: Cerebrospinal fluid; RCT: Randomised controlled trial; TBM: Tubercular meningitis.

### 3.4. Sensitivity analysis

Schoeman et al. studied the role of aspirin in childhood tubercular meningitis. This study was different from other two studies included in terms of younger age of patients (12−54 months) and duration of aspirin therapy (only one month). So, we evaluated the results after excluding this study.

Aspirin when compared to placebo was significantly better in terms of reduction in new onset stroke with hazard ratio of 0.45 (95% CI of 0.25−0.80, $p = 0.006$) (Fig. 6). The test for heterogeneity, $I^2$ was 0%, indicating that there was no or minimal heterogeneity or inconsistency in the studies included. However, significant difference was not found on mortality and composite outcome (Figs. 5 and 7).

Sensitivity analysis was also performed with all the four studies (Mai et al., Misra et al., Schoeman et al. and Amin et al.). Addition of this study [8] showed similar results that aspirin did not significantly reduce mortality in patients with tubercular meningitis in comparison to placebo [hazard ratio of 0.75 (95% CI of 0.51−1.09, $p = 0.57$)].

### 3.5. Risk of bias assessment

Full details of the risk of bias assessment have been outlined in Table 2 and Fig. 8.

All the included studies described randomization methods and were considered low risk. Information about allocation concealment and blinding of participants was provided in all studies and were considered low risk except Misra et al., which was an open label study and was considered high risk. Information about blinding of outcome assessor was unclear for all trials and were considered unclear risk. All the trials were double blinded except one Misra et al., which was open label.

### 3.6. Safety assessment

Misra et al. [5] observed 33 adverse events in total which included vomiting in 28 patients, epigastric discomfort in 1 patient, rashes in 4 patients and jaundice, altered liver function in 28 patients. But, the authors did not provide the adverse events separately in individual study arms. However, they mention that there is no difference in adverse effect profile of aspirin and placebo group.

Mai et al. [6] observed no significant difference in gastro-intestinal bleeding or MRI proven intracranial bleeding event in placebo, low dose aspirin (81 mg) and high dose aspirin (1000 mg) groups [13.9% in placebo versus 22.9% in low dose aspirin versus 20.0% in high dose aspirin]. There was no statistically significant difference in terms of grade 3 or 4 adverse events in placebo, low dose aspirin and high dose aspirin groups [26.8% in placebo versus 43.6% in low dose aspirin versus 22.5% in high dose aspirin]

Schoeman et al. [9] also reported that aspirin was well tolerated but one death was probably related to aspirin in a patient who deteriorated neurologically during fourth week of treatment and died because of intracranial hemorrhage. One patient was excluded from the study due to hematemesis after first dose. But, they did not report adverse events in placebo arm and did not mention whether these patients belonged to low dose or high dose group. The details of other adverse events were not mentioned (Table 3).

### 3.7. Discussion

The meta-analysis from randomized controlled trials evaluating efficacy and safety of aspirin as an adjunctive therapy in tuberculosis meningitis over and above anti-tubercular therapy did not show significant reduction of mortality (primary outcome) or composite outcome of mortality and new onset stroke. However, aspirin significantly reduced new onset stroke as compared to placebo in patients with tubercular meningitis [hazard ratio of 0.51 (95% CI

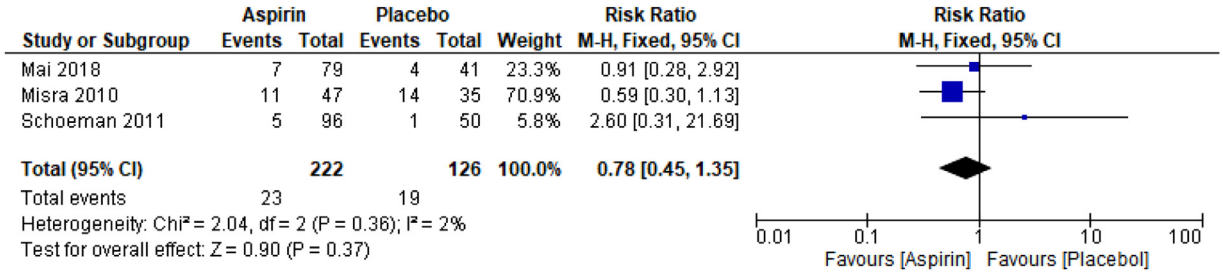


**Fig. 2.** Effect on mortality.

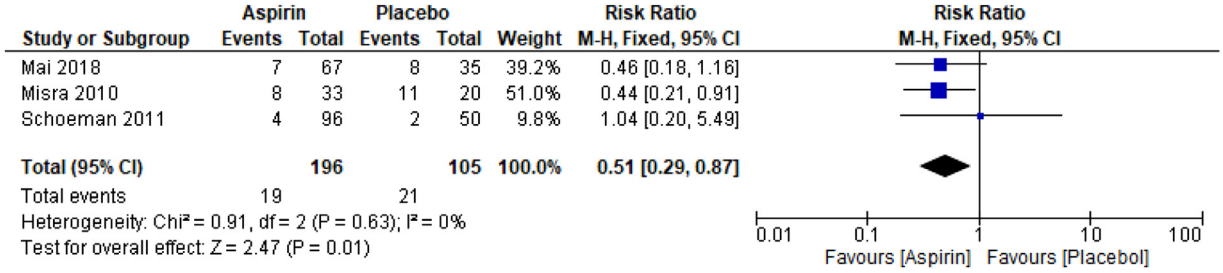


**Fig. 3.** Effect on stroke.

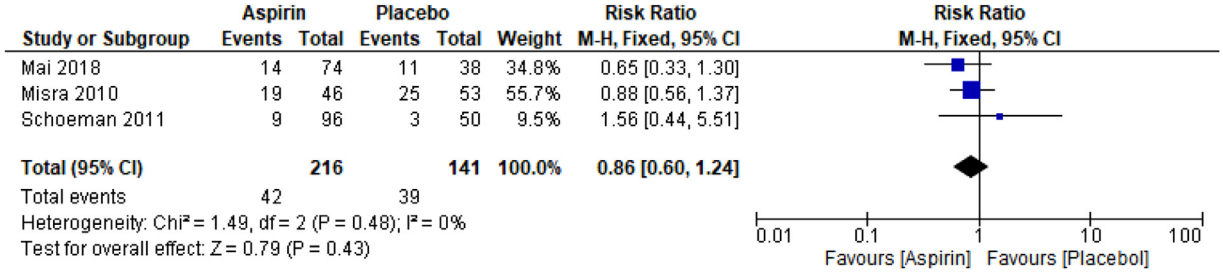


**Fig. 4.** Effect on composite outcome (New Onset Stroke + Mortality).

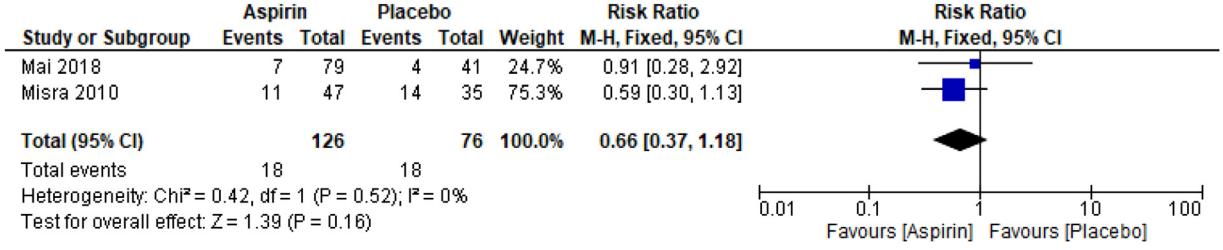


**Fig. 5.** Sensitivity analysis showing effect on mortality.

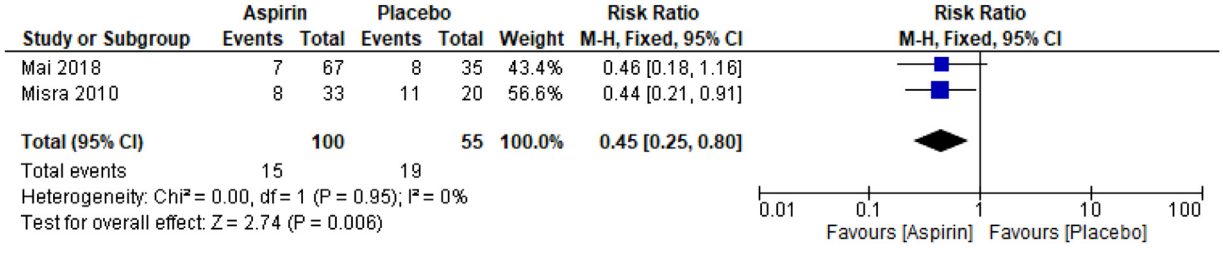


**Fig. 6.** Sensitivity analysis showing effect on new onset stroke.

0.29–0.87, $p = 0.01$)], with Number Needed to Treat (NNT) = 10. Sensitivity analysis of Mai et al. and Misra et al. also showed similar results i.e. significant reduction was not seen in mortality or composite outcome but there was statistically significant reduction in aspirin as compared to placebo in terms of new onset stroke. Since one of the main complication of tubercular meningitis is cerebral stroke (with reported incidence ~13–57%), which can lead to poor clinical outcome [3,10]. Also, the mortality is about three times higher in

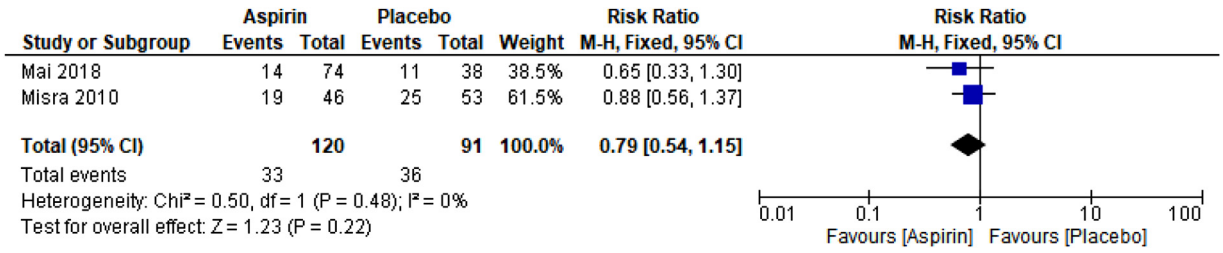


**Fig. 7.** Sensitivity analysis showing effect on composite outcome (New Onset Stroke + Mortality).

**Table 2**
Risk of bias assessment in included studies.

| Study | Selection bias (Random sequence generation) | Allocation bias | Performance bias (Blinding of participants and personnel) | Detection bias (Binding of outcome assessment) | Attrition bias (Incomplete outcome data) | Reporting bias (selective reporting) |
|---|---|---|---|---|---|---|
| Mai et al. [6] | Low risk | Low risk | Low risk | Unclear risk | Unclear risk | Unclear risk |
| Misra et al. [5] | Low risk | High risk | High risk | High risk | Unclear risk | Unclear risk |
| Schoeman et al. [9] | Low risk | Low risk | Low risk | Unclear risk | Unclear risk | Unclear risk |

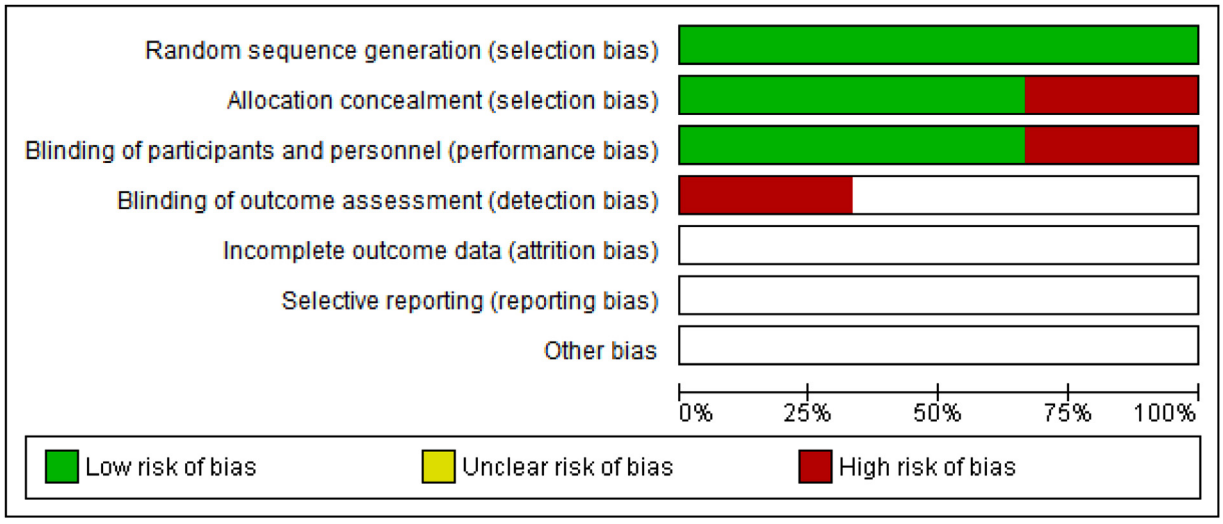


**Fig. 8.** Bias assessment of the studies included for analysis.

**Table 3**
Safety assessment summary.

| Study | GI bleeding or MRI proven new intracranial bleed | Others |
|---|---|---|
| Mai et al. | Placebo group: 5/36<br>Low dose group: 8/35<br>High dose: 8/40 | Did not report any other adverse effect |
| Schoeman et al. | GI Bleeding in Aspirin: 1, Placebo: Not reported<br>MRI proven new intracranial bleed in Aspirin: 1, Placebo: Not reported | Melena, Raised transaminases, Reye syndrome: None in aspirin group.<br>Placebo: Not reported |
| Misra et al. | None in both groups | Vomiting: 28<br>Epigastric discomfort: 1<br>Rashes: 4<br>Raised transaminases: 28 |

young tubercular meningitis patients with stroke compared to those without [3,10]. So, even the NNT of 10 could have potential clinical significance in terms of mortality reduction and prevention of new onset stroke, thus prevention of disability.

Since TBM is a hypercoagulable state with decrease protein *S* and increase in factor VIII [2], aspirin due to its antiplatelet action can inhibit platelet aggregation at low doses (75–150 mg) and due to this property can prevent ischemic cerebrovascular events like new onset stroke. However, at high doses (> 150 mg), aspirin has anti-inflammatory action by inhibiting pro-inflammatory prostaglandins and TxA2 which could be beneficial in reducing intra-cerebral inflammation in these patients. The trials included in our study used aspirin at both low and high doses. Mai et al. and Schoeman et al. explored beneficial effects of both low dose and high dose. However, the low

and high doses in both was not uniform. Mai et al. used low dose as 81 mg and high dose as 1000 mg. Schoeman et al. used low dose as 75 mg and high dose as 100 mg/kg/day. Whereas Misra et al. used only low dose of aspirin 150 mg. The dose selection in all the three studies appears to be arbitrary without any scientific explanation on its rationale.

Aspirin was safe and was well tolerated at both low dose (81 mg) as well as high dose (1000 mg). The studies included did not find any statistically significant difference in GI bleeding, intracranial bleeding and grade 3 or 4 adverse events when compared to placebo. Misra et al. do not provide detailed information on adverse effects separately in aspirin and placebo arms separately so we could not perform analysis of safety data. Also, the studies were not powered to detect these differences.

An earlier meta-analysis by Rizvi et al. [7] showed that aspirin reduces the risk of new infarctions in patients with tubercular meningitis but do not reduce mortality. This meta-analysis had additionally included an open label study in children [8] which enrolled only patients with severe TBM (stage III) but the diagnosis was unconfirmed. The duration of aspirin was not clearly mentioned in this study. This study also did not include new onset stroke as an outcome although it did include mortality. Due to various shortcomings inclusion of this study into the meta-analysis is likely to reduce the quality of the meta-analysis. Nevertheless, we conducted a sensitivity analysis by including this study by Amin et al. [8] but it did not change the results.

The major limitations of our meta-analysis is that only three randomized controlled trials were included. Since, only three RCTs are available so there is lack of robust data to support the conclusion. Misra et al. do not provide detailed safety information of both groups so we could not perform safety analysis. The other limitation is that the time point of outcome analysis is not uniform across the three studies (Misra et al. analyzed outcome at 3 months; Mai et al. at 2 months and Schoeman et al. at 6 months). The drug, dose and duration of adjunctive medications (aspirin and steroids) across the studies are also different. Also, publication bias could not be assessed because only three studies were included in the meta-analysis.

Although this meta-analysis did not show significant reduction in mortality and composite outcome (mortality and new onset stroke) with aspirin as compared to placebo but there was significant reduction in new onset stroke in aspirin group as compared to placebo which might be of clinical importance in management of patients with tubercular meningitis. Hence, a large well conducted RCT is required to add to existing knowledge and clarify role of aspirin as adjunctive treatment in patients with tubercular meningitis.

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## Author contributions

Rohilla R: Literature search, Data extraction, Risk of bias assessment, Data analysis, Manuscript writing and editing.

Shafiq N: Data verification, Manuscript review, Supervision and important intellectual input.

Malhotra S: Conceptualisation, Data verification, Manuscript review and intellectual input.

## Data sharing statement

No restrictions on the datasets.

## Declaration of Competing Interest

No conflict of interest.

## Acknowledgment

None.

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