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Review Article

Safety and Efficacy of Mannitol in Treatment of Cerebral Malaria: A Systematic Review of Randomized Control Trials

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Abstract

Cerebral malaria is one of the leading causes of death and disability in Sub-Saharan Africa. It is characterized by convulsion, sustained coma due to brain swelling, debilitating neurological complications, behavioral and cognitive disturbances. It is associated with a high morbidity and mortality especially in children, posing high demand for highly effective, curative, and long-lasting therapies. Cerebral malaria is a medical emergency that requires urgent treatment to prevent related mortality and disabilities. It is primarily treated with artesunate as par current WHO recommendation; however, other form of parenteral anti-malarials like quinine can be used. Additionally, many adjunctive therapies were used, especially in countries where the disease is endemic. One of these therapies is the mannitol, which is an osmotically active drug that can lower intracranial pressure by absorbing extracellular fluid into the vascular compartment. Therefore, to determine the safety and efficacy of mannitol in the treatment of cerebral malaria, we systematically searched published data from main databases including PubMed, PubMed Central, Google Scholar, ScienceDirect, and Medline. Two research registries were also searched: the Cochrane Registry and clinicaltrial.gov. Data was collected after applying inclusion and exclusion criteria and studies were appraised critically. Both Medical Subject Headings (MeSH) and regular keyword search strategies were employed. The review findings indicated that mannitol therapy is safe and relative effective when used early in children less than five years, but comparably harmful when used in older adults especially when co-associated with other factors like hypertension, hypocholesterolemia, smoking and excessive alcohol consumption.

Key Words: ovale, vivax; malaria and knowlesi; anti-malarial

Introduction

Malaria is a vector-borne parasitic disease caused by plasmodium species and transmitted by the bite of female anopheles' mosquito. There are currently five recognized plasmodium species that can cause malaria: plasmodium falciparum, ovale, vivax, malaria and knowlesi (Ashley, Pyae Phyo, & Woodrow, 2018). Malaria is more common and endemic in tropical and subtropical countries with devastating consequences on health and economy. An estimated 212 million malaria cases occurred globally in the year 2015 with over 90% of the cases occurring in African countries, 7% of the cases in South East Asia and less than 2% of the cases occurred in Eastern Mediterranean Region. As of 2015, the malaria related mortality was estimated to be 429,000 cases globally, 92% of which occurred in African region and virtually all the deaths (99%) were plasmodium falciparum related (WHO, 2016). Based on clinical features, malaria is classified into two main types: uncomplicated and complicated or severe malaria. The former present with non-specific signs and symptoms including fever, myalgia, headache, and diarrhea or vomiting. Whereas the later presents with serious clinical syndromes including hyperpyrexia, convulsion, confusion, abnormal breathing, jaundice, anuria or features of cerebral impairment (Ashley et al., 2018).

Cerebral malaria is the most serious and fatal form of severe malaria which has high morbidity and mortality, almost 100% fatal if treatment not instituted early. World Health Organization (WHO) defined cerebral malaria as a state of unarousable coma, commonly associated with convulsion, lasting more than an hour with Glasgow coma score <11 in adults or a Blantyre coma score <3 in children with evidence of peripheral malarial hyper-parasitaemia and after exclusion of other causes of coma like viral or bacterial meningitis, electrolyte disturbances, anemia or hypoglycemia (Dvorin, 2017). It usually occurs within two weeks after bite with anopheles' mosquito or within seven days after development of malarial fever. It has poor prognosis with long term neurologic sequelae, behavioral and cognitive disturbances. It is commonly associated with brain swelling, seizures, blindness and other forms of retinopathies (Rénia et al., 2012). It is more common in children; however, it occurs in adults with slightly different patterns due to age differences, host or parasite disposition, pattern of exposure or health services delivery (WHO, 2014). Cerebral malaria is a medical emergency that requires urgent treatment to

prevent related mortality and disabilities. It is primarily treated with artesunate as par current WHO recommendation; however, other form of parenteral anti-malarials like quinine can be used. Follow up medications in form of artemesinin based combination therepies are given to prevent recurrence (Ziaul-Islam & Rahman, 2015). Additionally, many therapies are currently employed as adjunctive treatment in patients with cerebral malaria and these include the use of mannitol, albumin, dexamethason, levamisole, arginine, erythropoetin and exchange blood transfusion (John, Kutamba, Mugarura, & Opoka, 2010).

Mannitol is a pharmacologically inert substance that is poorly reabsorbed in the kidney but osmotically active drug that can lower intracranial pressure by absorbing extracellular fluid into the vascular compartment. It is commonly used to reduce brain swelling in surgical patients with raised intracranial pressure due to cerebral edema following post-traumatic head injury (Ichai et al., 2009). It has demonstrable beneficial effects in children with Reye's syndrome and its use among patients with cerebral malaria has been advocated by several authors but the efficacy and safety has not been established (Okoromah, Afolabi, & Wall, 2011). In view of this, the importance of a scientific review that would qualitatively determine the safety and efficacy of mannitol in treatment of cerebral malaria cannot be overemphasized. Only one qualitative literature review study was done previously by Cochrane library but left with huge gap in which the study did not categorically establish the efficacy and the side effects of mannitol in treating cerebral malaria. Additionally, the study is not restricted to mannitol only but included other therapies with other osmotic diuretics in the analysis; therefore, this study is the first qualitative literature review that assesses the safety and efficacy of mannitol in treatment of cerebral malaria. Countries where malaria become endemic are still using mannitol as adjunctive therepy for treatment of cerebral malaria despite lack of consensus or guidelines from national or international professional bodies. Therefore, a review that will assess the safety and efficacy of mannitol in treatment of cerebral malaria is extremely important. In this review, we aimed to test the hypothesis that 'mannitol improves clinical outcomes in patients with cerebral malaria'.

2. Method

2.1. Study Design and Protocol

A systematic review of published literatures on mannitol use in the treatment of cerebral malaria. The protocol used for this study was based on the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)'.

2.2. Data Collection

Major electronic databases were searched for relevant information which include PubMed, PubMed Central, Medline, ScienceDirect and Google Scholar. Two research registry comprising of Cochrane central register (Cochrane library 2020 issue 4) and clinicaltrial.gov (www.clinicaltrials.gov) were searched for relevant clinical trials. A search of the reference lists of the included articles for related articles was conducted and effort was made to search unpublished literatures by contacting experts. The following key words were used as search content for identification of relevant data: "mannitol" AND "cerebral malaria" AND "randomized trials", "cerebral malaria" AND "adjunctive therapy" AND "randomized trials", "randomized trials" AND "cerebral malaria" AND "treatment".

2.3. Inclusion and Exclusion Criteria

The following inclusion criteria were used: 1) any randomized trials on mannitol treatment in cerebral malaria 2) studies done exclusively on cerebral malaria 3) studies done exclusively on humans 4) studies done in English or translated into English. Any study that combine mannitol and any other adjunctive therapy were excluded.

2.4. Population

We included patients with cerebral malaria as defined by WHO regardless of their age, sex or country of origin.

2.5. Intervention

The intervention we included is the use of mannitol as adjunctive therapy for cerebral malaria in addition to the standard antimalaria therapy.

2.6. Comparison

Patients with cerebral malaria who received mannitol as adjunctive therapy were compared with control groups who received only standard antimalarial treatment with or without placebo.

2.7. Outcome

We aimed to assess the following primary outcomes: mortality, systemic complications and neurologic sequelae. The secondary outcomes of interest include regain of consciousness, duration of hospitalization, ability to take orally, and cardiopulmonary compromise.

2.8. Data Extraction

A standard data extraction form was used for data extraction from the included studies in which the following information were extracted from both the intervention and control group: authors' details, publication year, sample size, demography of the study population, dose of the mannitol, type of the antimalarial used and dose, route of administration, outcomes data and follow up period.

2.9. Risk of Bias Assessment

The risk of bias was determined based on the following domains: random sequence generation, allocation concealment, patient blind and care provider blind, intention to treat analysis, outcome assessor blind, incomplete outcome data and selective outcome reporting (Estellat C, Torgerson DJ, 2009). Each domain is graded as high, moderate or low with information from the study paper justifying our judgment.

2.10. Quality Assessment

CASP Checklist (2018) for Randomized Controlled Trials was used for assessing the validity of the included randomized control trial studies(CASP Checklist RCT, 2018) which contain 11 questions that assess the validity and effectiveness of the study results. A score of >7 was considered as a high-quality paper, 5-7 a moderate quality and <5 was considered as low-quality paper.

3. Results

3.1. Literature Search

A search of multiple electronic databases yielded 513 articles. 16 articles from PubMed, 144 from PubMed Central, 122 from Medline, 155 from Google Scholar, 71 from ScienceDirect, 3 from Cochrane database registry and 2 from clinicaltrial.gov registry. Nine articles were selected for possible inclusion after review of abstracts and the remaining 504 articles were found to be irrelevant to the study and therefore discarded. After full text review of the 9 articles, only 2 articles were found to have met the inclusion/exclusion criteria and thus included in the meta-analysis with the remained 7 articles been removed. The 2 articles were subjected to critical appraisal and were found to be assessed as high-quality papers. Therefore, only two articles were included in the meta-analysis **(figure 1).**

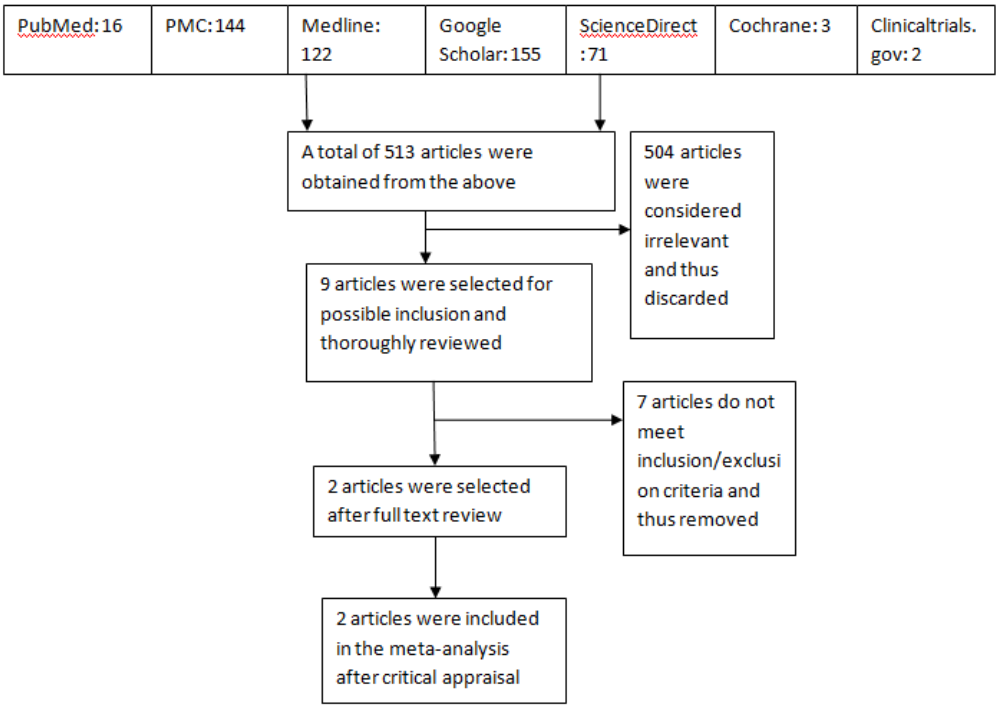

Figure 1: Flowchart of the study selection

3.2. Study Characteristics

Only two studies were identified to have met the criteria for inclusion in this review. The first paper (Namutangula, Ndeezi, Byarugaba, & Tumwine, 2007) was a randomized double blind placebo clinical trial on children between 6 month to five years, while the second paper (Mohanty et al., 2011) is a randomized open label non-placebo clinical trial on individuals who are 16 yrs old or older. Both studies were done on patients with cerebral malaria as par WHO definition of cerebral malaria. In the first study, the total sample size was 156 subjects: 80 subjects in the controlled group and 76 in the intervention group. The total male and female subjects were 80 and 76 subjects respectively. The minimum age of the participants in the first study was 6 months and the maximum age was 5yr. The total sample size of the second study was 61 subjects: 31 subjects in the controlled group and 30 in the intervention group. There are 30 male subjects and 31 female subjects entirely. The minimum age of the participants in the second study was 16 yr and the maximum age was 36yr.

3.3. Dosing

In both studies, all patients received quinine as the malaria treatment which was given intravenously at the dose of 10mg salt/kg body weight in 10mls/kg of 5% dextrose 8hrly till awake. This is then followed by oral quinine 10mg salt/kg 8hrly for 7days. However, some patients received a loading dose of intravenous quinine of 20mg salt/kg body weight. All the patients in the intervention group in both studies received intravenous 20% mannitol at a dose of 1g/kg over 20mins in the first study, and 1.5g/kg over 15mins followed by 0.5g/kg 8hrly for 72hrs in the second study.

3.4. Risk of Bias Assessment

2.4.1. Allocation: Both studies mentioned that randomization occurred with sequence generation. The method of randomization was mentioned and was said to be done in blocks of variable sizes (4-10) in the first study and blocks of 20 in the second study. Allocation was concealed in both the studies and none of the subject's refused participation after allocation.

2.4.2. Blinding: The first study was blinded and the method of blinding was double blinding involving blinding of both the patients and the investigators with blinding of outcome assessment. The second study was open label; however, it was not clear who was not blinded: patients, investigators or outcome assessors or all were not blinded.

2.4.3. Follow Up: In both studies, the maximum duration of follow up was up to the time of discharge which was a maximum of 7 days and patients were not followed after discharge. All participants completed the duration of the hospital stay up to the discharge and only one participant was lost to follow up who was also included in the final analysis.

3.5. Outcome Assessment

2.5.1. Primary Outcome: In the first paper, there were a total of 9 patients that have died in the intervention (9/66) making a proportion of 13.6%; whereas, a total of 13 patients died in the control group (13/67) making a proportion of 19.4%. In the second paper, there were 9 patients that have died in the intervention group (9/30) with a proportion of 30%, and 4 patients died in the control group (4/31) with a proportion of 13%. In both papers, none of the participants has any systemic complications or neurologic sequelae.

2.5.2. Secondary Outcomes: In the first paper, the average time to regain consciousness was shorter in the intervention group (18.9hrs) than in the control group (20.5hrs), but in the second paper it was found to be shorter in the control group (32hrs) than in the intervention group (90hrs). In both studies the duration of hospital stay was reported to be 7days, but none of the two studies reported cardiopulmonary compromise. However, the time to begin oral intake was reported in the first study and was shown to be shorter in the mannitol group (34.0hrs) than in the placebo group (40.0hrs).

4. Discussion

Both papers have low risk of bias as the methods of randomization were clearly mentioned. The adequate allocation concealment in the study eliminated selection bias which indicates good quality. In this review, it is apparent that there were clear differences in the themes and variables reported across the two studies. In the first study, which involved patients aged between 6 months to five years, the use of mannitol in the treatment of cerebral malaria was relatively safe and effective. This finding was also reported in study by Sekarningrum and colleagues, where early mannitol administration was shown to have improved outcomes in pediatric patient with cerebral edema, though cause of the edema was not categorically described in the study (Sekarningrum et al., 2018). However, in the second study, which involved adult patients aged ≥ 16yr, the use of mannitol in the treatment of cerebral malaria was generally unsafe and can be considered as harmful due to modest increase in mortality and prolong duration of coma among intervention group as compared to controlled group. Many reasons could be accounted for the effect dichotomy between the two studies.

Firstly, the age differences between the subjects in the two studies could be an important factor in determining the safety and efficacy of mannitol therapy in cerebral malaria. In many preclinical studies, increasing age has been identified to be associated with increased size of cerebral infarction that may subsequently result in cerebral edema (Idro, Jenkins, & Newton, 2005). This could explain the observed effects in the second study that showed a trend of increased mortality and longer duration of coma in the intervention group than control group. Additionally, the coma of cerebral malaria is more likely to develop from multiple etiologies in adults than in children (Newton & Warrell, 1998). For example, cerebral edema and raised intracranial pressure may occur concomitantly which may result into coma. In this case, for example, the mannitol would handle the cerebral edema but might not have effect on the raised intracranial pressure and therefore leading to prolong coma duration. Also, the double blinding in the first study eliminated outcomes bias, whose absence in the second paper increased risk of the bias which could be attributed to the effects observed in the second study.

Secondly, intracerebral hemorrhages and lacunar infarctions have been described in the pathophysiology of cerebral malaria which could lead to microvascular obstruction. Thus, introduction of hyperosmolar solution like mannitol could further exacerbate the fluid exchange in the already compromised microcirculation (Newton & Warrell, 1998). The risk factors for these pathologic findings include old age, hypertension, smoking, excessive alcohol consumption, hypocholesterolemia and drugs (Pongponratn et al., 2003). These factors are more common in adults than in children further explaining the differences in the safety and efficacy of the mannitol across the two studies. Thirdly, the dose used in the second study (1.5g/kg start followed by 0.5g/kg 8hrly) is actually low to observe the beneficial effects of mannitol in adults, which can be compared with the dose used in the first study (1g/kg 8hrly). The doses of mannitol used in many studies ranges between 0.25g/kg to 2.5 g/kg, and studies that uses higher doses showed relative higher efficacy of using mannitol as adjunctive therapy in the treatment of cerebral malaria. However, higher doses of mannitol could significantly affect renal function and therefore, care has to be taken when prescribing high dose by monitoring renal function (Mohanty, Patel, Pati, & Mishra, 2006).

Conclusion

The safety and efficacy of mannitol as adjunctive therapy in the treatment of cerebral malaria has shown different therapeutic profile in this review. Based on the findings, it can be hypothesized that use of mannitol in patients with cerebral malaria is relatively safe and effective when used in children less than five years due to the trend of improvement observed in the first study among the intervention group more than the controlled group. However, it is comparatively harmful and ineffective when used in older patients due to the increased mortality rate and longer duration of coma recovery period observed in the second study among the intervention group more than in the controlled group. Therefore, we hypothesized that early use of mannitol as adjunctive therapy in the treatment of cerebral malaria in children less than five years is relative safe and can improve patient outcome, reduce duration of coma, decrease rate of neurologic complications and facilitate early discharge from the hospital. We also hypothesized that mannitol should not routinely be used in older patients and when necessary, certain risk factors should be rule out first including advancing age, hypertension, hypocholesterolemia, drug abuse, smoking and excessive alcohol consumption. However, more randomized clinitical trial studies are needed to ascertain the safety and efficacy of the drug in cerebral malaria treatment in any age group.

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