Mannitol and other osmotic diuretics as adjuncts for treating cerebral malaria (Review)

Okoromah CAN, Afolabi BB

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[Intervention Review]

Mannitol and other osmotic diuretics as adjuncts for treating cerebral malaria

Christy AN Okoromah[1], Bosede B Afolabi[2]

[1]Department of Paediatrics and Child Health, University of Lagos, Lagos, Nigeria. [2]Department of Obstetrics and Gynaecology, University of Lagos, Lagos, Nigeria

Contact address: Christy AN Okoromah, Department of Paediatrics and Child Health, University of Lagos, College of Medicine, Idi-Araba, Lagos, PMB 12003, Nigeria. christyok@operamail.com.

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ABSTRACT

Background

The main treatment for cerebral malaria is parenteral antimalarials. Mannitol and urea are used as adjunct therapy for cerebral malaria, but the World Health Organization does not recommend them.

Objectives

To compare mannitol or urea to placebo or no treatment for treating children and adults with cerebral malaria.

Search strategy

We searched the Cochrane Infectious Diseases Group Specialized Register (May 2006), CENTRAL (*The Cochrane Library* Issue 3, 2006), MEDLINE (1966 to May 2006), EMBASE (1974 to May 2006), LILACS (1982 to May 2006), and reference lists of articles. We contacted relevant organizations and researchers.

Selection criteria

Randomized and quasi-randomized controlled trials comparing mannitol or urea to placebo or no treatment in children and adults with cerebral malaria.

Data collection and analysis

No trials met the inclusion criteria.

Main results

No trials met the inclusion criteria.

Authors' conclusions

We identified no randomized or quasi-randomized controlled trials to support or refute the use of mannitol or urea as adjuncts for treating cerebral malaria in clinical practice. This is likely to require a multicentre trial.

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PLAIN LANGUAGE SUMMARY

Mannitol and other osmotic diuretics as adjuncts for treating cerebral malaria

Plain language summary pending.

BACKGROUND

Cerebral malaria is a life-threatening complication of severe falciparum malaria. It accounts for significant morbidity and mortality in African children and non-immune travellers. Cerebral malaria associated mortality rates range between 10% and 50% with an average case fatality rate of 16% (Murphy 2001), and 2% to 10% of treated childhood survivors experience cerebral malaria associated neurological disabilities that last for over 6 months (Murphy 2001; Warrell 1982; White 1992).

Although the causes of death and neurological disabilities in cerebral malaria are multifactorial and often undetermined, raised intracranial pressure has been associated with a poor outcome in African children (Newton 1991; Newton 1997; Waller 1991). Sporadic reports implicating raised intracranial pressure in malaria were made in the 1940s and 1950s (Rothe 1956). Autopsy findings from Nigerian children with cerebral malaria have shown frank cerebellar tonsillar herniation or coning (Walker 1992) — a downward compression of the lower posterior part of the brain tissue and its vital structures that results in a protrusion out of the skull through an opening at the base of the skull (foramen magnum) — that can lead to cardiopulmonary arrest and death. Computed tomography (CT) in Kenyan children with cerebral malaria showed a wide range of appearances including diffuse brain swelling associated with neurological deficits in some of the cases (Newton 1994a). Similarly, CT and magnetic resonance imaging (MRI) studies on Thai adults with cerebral malaria have reported features of raised intracranial pressure (Looareesuwan 1993; Looareesuwan 1995), albeit mild cerebral swelling and localized cerebral oedema (brain swelling) associated with focal lesions such as infarction or haemorrhage (Millan 1993; Pham-Hung 1990). Recently, CT findings in adult cerebral malaria found diffuse cerebral oedema to be the most common abnormality in 67% of patients studied (Patankar 2002). They concluded that abnormalities of CT scans in adults with cerebral malaria are common as well as variable and may conform to four characteristic patterns: a normal scan, isolated diffuse cerebral oedema, diffuse cerebral oedema with bilateral thalamic hypoattenuation, and diffuse cerebral oedema with bilateral thalamic and cerebellar hypoattenuation, without areas of petechial haemorrhages, which are the hallmark of cerebral malaria at pathologic examination. Overall, several authors now suggest that cerebral oedema, which may be associated with neurological deficits and death, is common in both childhood and adult cerebral malaria, but it is not invariably a terminal event (Looareesuwan 1993; Looareesuwan 1995; Newton 1991; Patankar 2002). Although cerebral oedema is not consistently found in all cases of cerebral malaria, the condition is more commonly seen in children below 5 years of age compared with adults, and reports show that there are differences in the clinical presentation and pathophysiology of brain swelling between children and non-immune adults (Mturi 2003; Okelo 1994).

Although raised intracranial pressure has been widely reported in children and adults with cerebral malaria, there are unresolved issues and controversy around its causes, mechanisms, pathophysiology, and prognostic importance. Most of the early investigators suggested that raised intracranial pressure in malaria was caused by cerebral oedema, but later reports postulated that it was caused by an increase in the brain's blood volume, probably from a combination of sequestration of parasitized (malaria infected) red blood cells in the brain vessels (cerebral capillaries and venules) and the movement of fluid from the intravascular space into the brain matter (Kingston 1971; Newton 1991; Newton 1997; Tomlinson 2003). People with severe malaria, particularly those with cerebral malaria and hypoglycaemia, may have raised levels of tumour necrosis factor (TNF). Researchers have speculated that TNF may increase the stickiness of the parasitized red blood cells and slow the blood flow in the brain (Grau 1989), which also lead to fluid shifts, increased metabolic rate, and increased cerebral blood flow and volume (Newton 1996; Newton 1997). These mechanisms form the basis for possible benefits that may be derived from using mannitol or other osmotic diuretics in cerebral malaria.

Osmotic diuretics

Osmotic diuretics, such as mannitol and urea, collectively describe a group of pharmacologically inert substances that are either incompletely re-absorbed or not re-absorbed in the kidneys. They increase the osmotic pressure of plasma and the kidney tubules and

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thereby restrict movement of water from the extracellular space (for example, blood vessels) into the interstitial space (for example, brain matter). Osmotic diuretics are relatively simple and cheap adjunct interventions that may improve the outcome of a large number of children and adults with cerebral malaria.

Mannitol

Mannitol is currently the most frequently used osmotic diuretic in several fields of medicine (Shenkin 1962). It is widely used in acute renal failure, glaucoma, post-traumatic intracranial hypertension, and non-traumatic encephalopathies such as Reye's syndrome. Reye's syndrome is an acute and often fatal childhood illness associated with severely impaired liver function and a rapidly progressing raised intracranial pressure due to brain swelling. This syndrome has many features common with cerebral malaria, and it responds favourably to mannitol (Minns 1991; Newton 1994b).
There have been reports that mannitol reduces mortality and morbidity in African children (Ghanaian and Kenyan) with cerebral malaria (Commey 1980; Newton 1997). However, it is difficult to determine the significance of these reports as they were not randomized controlled trials and lacked appropriate controls. Other reports suggest that although the beneficial effect of mannitol may be transient, that in resource-limited settings where intensive care monitoring and nursing are often lacking, shortening the coma recovery time may have benefits for neurological disabilities (Tomlinson 2003). Mannitol has also been demonstrated to have suppressive effects on free radicals and nitric oxide, which have been implicated in the pathophysiology of cerebral malaria and neurological abnormalities (Grau 1989; Ho 1998).
Mannitol is administered intravenously. Because it causes the extracellular space to expand, it may have some undesirable effects such as cause or worsen heart failure and pulmonary oedema, shock from excessive diuresis, headaches, nausea, and vomiting.

Urea in invert sugar

Urea in 10% invert sugar has been used to treat cerebral malaria associated cerebral oedema. It may be given orally or intravenously; oral preparations are notable for their foul taste and gastrointestinal side effects.
Two studies reported that urea improved the outcome in Liberian children, but these studies lacked appropriate controls (Kingston 1971; Rothe 1956). However, this drug is no longer used because of side effects such as thrombosis, tissue irritation and damage following extravasations, and elevation of serum ammonia levels in people with deranged liver function.
Presently, there is no consensus on the use of mannitol or urea as adjuncts for treating of cerebral malaria, and the World Health Organization does not recommend their use in cerebral malaria (WHO 1990; WHO 2000). Most reports that claim either beneficial or harmful effects are not randomized controlled trials. In countries that are most burdened by cerebral malaria, such as Nigeria, these drugs in combination with standard antimalarial treatment, appropriate fluid therapy, and supportive nursing care still constitute the main approach to treating cerebral malaria, although there may be wide institutional variations. In such countries, adjunct interventions that improve outcomes in cerebral malaria associated raised intracranial pressure are likely to have important health benefits. The need to provide evidence for benefits or harms of mannitol or urea in cerebral malaria prompted this review.

OBJECTIVES

To compare mannitol or urea to placebo or no treatment for treating children and adults with cerebral malaria.

Null hypothesis: There is no difference in effectiveness or adverse events between mannitol or urea and placebo or no treatment, as adjuncts for treating raised intracranial pressure in cerebral malaria.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials.

Types of participants

Hospitalized children and adults:

- with clinical syndromes of cerebral malaria and parasitologically confirmed malaria, in whom meningitis and other causes of unconsciousness have been excluded (WHO 2000); and
- receiving standard antimalarial treatment for cerebral malaria.

Types of interventions

Intervention

Mannitol or urea.

Control

Placebo or no treatment.

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Types of outcome measures

Primary

- Death.
- Life-threatening complications (repeated convulsions, heart failure, pulmonary oedema, and systemic hypertension).
- Major neurological sequelae 6 months or more post-randomization (for example, blindness, deafness, speech or learning difficulties, paralysis of the limbs, or any other neurological deficit pre-specified by the trial authors).

Secondary

- Coma recovery time (time to regain full consciousness defined as time between onset of coma and its resolution or as defined by the trial authors).
- Length of stay in hospital (period from admission to discharge).
- Need to support ventilation.
- Need for cardiopulmonary resuscitation.

Adverse events

- Adverse events sufficient to cause withdrawal from treatment, such as hypovolaemia (shock), acute renal failure, circulatory overload, pulmonary oedema, persistent vomiting; or any pre-specified adverse event by the trial authors.

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Databases

We searched the following databases using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register (May 2006); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (Issue 3, 2006); MEDLINE (1966 to May 2006); EMBASE (1974 to May 2006); and LILACS (1982 to May 2006).

Researchers and organizations

We contacted individual researchers working in the field and the following institutions and organizations for unpublished and ongoing trials: World Health Organization Roll Back Malaria Partnership (http://www.rbm.who.int/); University Infectious Diseases Departments in countries where malaria is endemic (Sub-Saharan Africa, Asia, and India); Medical Research Council, The Gambia; Kenya Medical Research Institute, Clinical Research Centre Kilifi, Kenya; and the National Institute of Medical Research, Ifakara Centre, Tanzania.

Reference lists

We checked relevant citations of all potentially relevant studies identified by the search strategy.

Data collection and analysis

We independently screened the results of the search to select potentially relevant studies and to retrieve the full articles. We independently applied the inclusion criteria to the potentially relevant studies. No randomized or quasi-randomized controlled trials met the inclusion criteria. Should any trials meet these criteria in the future, we will use the plan described in Appendix 2 to assess their eligibility and methodological quality, and to extract and analyse the data.

RESULTS

Description of studies

There were no randomized or quasi-randomized controlled trials comparing mannitol or urea with placebo or no treatment for cerebral malaria.

Risk of bias in included studies

No trials met the inclusion criteria.

Effects of interventions

No trials met the inclusion criteria.

DISCUSSION

We identified no randomized or quasi-randomized controlled trials on the efficacy and safety of mannitol or urea as adjuncts for treating cerebral malaria. The World Health Organization does not recommend these interventions for treating cerebral malaria. The basis for this recommendation needs to be strengthened by conducting a randomized controlled trial, which should ideally

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be prospective, multicenter, and include large number of participants. We are aware of two observational studies, one case series, and one uncontrolled clinical trial conducted in African children with cerebral malaria using urea plus dexamethasone or mannitol (Kingston 1971; Newton 1997). One author reported that intracranial hypertension is a consistent feature of cerebral malaria in African children and suggested that mannitol improved outcomes (Newton 1997), while the effects of urea with dexamethasone were described as "dramatic" in the case series (Kingston 1971). However, the small sample sizes and other methodological limitations of these studies preclude any definite conclusion on the effects of treatment. Also, there will be need to complement pragmatic clinical criteria for raised intracranial pressure with actual monitoring of cerebrospinal fluid pressure by spinal fluid manometer as well as imaging studies and autopsy brain examination.

Implications for research

Intracranial hypertension may be a modifiable complication of cerebral malaria that may lead to neurological disability or death, and osmotic diuretics such as mannitol may be effective in managing it. However, emerging evidence of raised intracranial pressure in children and adults with cerebral malaria could support arguments of potential benefit and thereby justify the need to subject the role of mannitol in cerebral malaria to a large, multicenter, randomized controlled trial.

Future trialists should use the World Health Organization's definition of cerebral malaria (WHO 2000), standard antimalarial treatment along with mannitol, and ensure appropriate trial design, outcomes, and analysis (Moher 2003). The clinical and laboratory criteria used to determine and define intracranial pressure levels should be clearly stated.

AUTHORS' CONCLUSIONS

Implications for practice

Currently, there is no evidence from randomized or quasi-randomized controlled trials to support or reject the use of mannitol or urea in clinical practice, as adjuncts for treating cerebral malaria in children and adults. However, with emerging evidence of raised intracranial pressure and its inherent morbidity and mortality, the continued use of mannitol or osmotic diuretics to treat cases of cerebral malaria complicated by cerebral oedema, in some practice settings may be justified pending the availability of evidence on their efficacy and safety.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

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DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Search methods: detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE (PubMed)[b]	EMBASE (DIALOG)[b]	LILACS[b]
1	mannitol	mannitol	MANNITOL	MANNITOL	mannitol
2	osmotic diuretics	osmotic diuretics	mannitolium	mannitolium	osmotic diuretics
3	cerebral malaria	1 or 2	mannitol	mannitol	1 or 2
4	brain malaria	cerebral malaria	manna	manita	malaria
5	severe malaria	severe malaria	manita	manna	cerebral malaria
6	-	4 or 5	mannityl	mannityl	4 or 5
7	-	3 and 6	mannomustine	mannomustine	3 and 6
8	-	-	nitromannite	nitromannite	-
9	-	-	nitromannitol	nitromannitol	-
10	-	-	osmitrol	osmitrol	-
11	-	-	osmofundin	osmofundin	-
12	-	-	1or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	1or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	-
13	-	-	exp MALARIA	exp MALARIA	-
14	-	-	MALARIA, FALCIPARUM	PLASMODIUM FALCIPARUM	-
15	-	-	MALARIA, CEREBRAL	MALARIA FALCIPARUM	-
16	-	-	MALARIA MENINGITIS	BRAIN MALARIA	-

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(*Continued*)

17	-	-	MENINGITIS, MALARIA	malaria	-
18	-	-	malaria	13 or 14 or 15 or 16 or 17	-
19	-	-	13 or 14 or 15 or 16 or 17 or 18	12 and 18	-
20	-	-	12 and 19	limit to human	-
21	-	-	limit to human	-	-

[a]Cochrane Infectious Diseases Group Specialized Register.

[b]Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Alderson 2004); upper case: MeSH or EMTREE heading; lower case: free text term.

Appendix 2. Planned review methods

Method	Details
Study selection	We will independently screen the results of the search to select potentially relevant trials and to retrieve the full articles. We will make efforts to ensure that multiple publications from the same data set were only used once. We will independently apply the inclusion criteria to the potentially relevant studies. We will base the inclusion criteria on the study design, type of participants, intervention, comparisons and outcome as described in the 'Criteria for considering studies for this review'. We will resolve any disagreements not clarified through discussion by consulting a third party. Where there is ambiguity, we will attempt to seek clarification from the trial authors and thereafter reassess the articles for inclusion. We will exclude studies that do not meet the inclusion criteria and state the reason in the 'Characteristics of excluded studies'.
Assessment of methodological quality (risk of bias)	We will independently assess the methodological quality of the included trials using generation of allocation sequence, concealment of allocation, blinding, and completeness of the trial. We will categorize the generation of allocation sequence and allocation concealment as adequate, inadequate, or unclear (Jüni 2001). For completeness of the trial, we will consider inclusion of 90% of participants as adequate. We will assess blinding as open (all parties are aware of treatment), single (the participant or care provider/assessor is aware of the treatment given), or double (trial uses a placebo or a double-dummy technique such that neither the participant or care provider/assessor know which treatment is given) blind. Blinding may not have been attempted in trials where different routes of administration are used. We will resolve any disagreements through discussion or by consulting a third party. Wherever necessary, we will contact trial authors for clarification.

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(*Continued*)

Data extraction	Where possible, we will extract data to allow an intention-to-treat analysis (the analysis should include all the participants in the groups to which they were originally randomly assigned). If the number randomized and the numbers analysed are inconsistent, we will calculate the percentage loss to follow up and report this information in a table. For binary outcomes, we will record the number of participants experiencing the event in each group of the trial. For continuous outcomes, we will extract information for each group to allow calculation of arithmetic means and standard deviations. If the data are reported using geometric means, we will extract information to calculate standard deviations on the log scale. We will extract medians and ranges and report them in tables.
Data analysis	We will stratify the analysis by type of osmotic diuretic. We will carry out statistical analyses using Review Manager 5. We will use risk ratios to interpret binary data, and combine continuous data using the mean difference. If there is evidence of skewed data, we will present these data in tables only. Where possible, we will extract time to event or censored data. We will use these to estimate the log hazards ratio and its variance within each trial, using methods proposed by Parmar 1998. We will assess heterogeneity amongst trials by visually examining the forest plots and by using the chi-squared test for heterogeneity using a 10% level (P value < 0.1) to provide evidence of statistically significant heterogeneity. Where it is appropriate to pool data, and heterogeneity is detected at P value less than 0.1, we will use the random-effects model. After including all the eligible studies in the primary analysis, we will conduct sensitivity analyses for each methodological quality factor (excluding blinding) using subgroups adequate, inadequate, and unclear. We will explore for evidence of publication bias and differences in methodological quality using a funnel plot. We do not intend to combine results of trials with different comparator drugs. Where the number of trials permit, we will investigate the following potential sources of heterogeneity using subgroup analyses or meta-regression: type of diuretic; participant age (children ≤ 18 years; adults (> 18 years); and coma score at study entry. We will explore for evidence of publication bias, differences in methodological quality, and heterogeneity of results using a funnel plot.

WHAT'S NEW

Last assessed as up-to-date: 11 May 2006.

18 August 2008	Amended	Converted to new review format with minor editing.

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HISTORY

Protocol first published: Issue 1, 2004

Review first published: Issue 4, 2004

12 May 2006	New search has been performed	New studies sought but none found.

CONTRIBUTIONS OF AUTHORS

Christy Okoromah identified and initiated the topic, wrote the protocol, and designed the eligibility and validity criteria. Bosede Afolabi commented on the protocol, and both reviewers discussed it and prepared the final version. CO and BA prepared the final review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.
- College of Medicine of the University of Lagos, Nigeria.

External sources

- Department for International Development (DFID), UK.

INDEX TERMS

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Medical Subject Headings (MeSH)

Diuretics, Osmotic [*therapeutic use]; Malaria, Cerebral [*drug therapy]; Mannitol [*therapeutic use]; Urea [*therapeutic use]

MeSH check words

Adult; Child; Humans

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