The Role for Osmotic Agents in Children with Acute Encephalopathies: A Systematic Review

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Abstract

Background - Raised intracranial pressure (ICP) is a common complication in children with acute encephalopathies. It compromises cerebral perfusion leading to ischaemia and may cause death when the brainstem is compressed during trans-tentorial herniation. Osmotic agents are widely used to control raised ICP. Their use in children is mainly guided by studies in adults.

Objective - We carried out this review to determine the best available evidence of the effectiveness of various osmotic agents and their effect on resolution of coma and outcome (neurological sequelae and mortality) in children with acute encephalopathies.

Selection criteria - We searched literature published between January 1966 and January 2008 on the use of osmotic agents in children aged between 0 and 16 years with acute encephalopathies.

Search strategy - We searched Medline, Cochrane Library, EMBASE, Cumulative Index to Nursing and Allied Health Literature and other databases for both published and unpublished literature.

Results - We identified four randomized controlled trials (RCTs), three prospective observational studies, two retrospective studies and one case report. The use of hypertonic saline appeared to achieve greater reduction in ICP compared to mannitol, normal saline and ringer’s lactate. This effect was sustained when it was given as a
continuous infusion. Boluses of glycerol and mannitol achieved transient reduction in ICP. Use of repeated doses of oral glycerol was associated with lower mortality and neurological sequelae when compared to placebo in children with acute bacterial meningitis. Hypertonic saline was associated with lower mortality when compared to mannitol in children with non-traumatic encephalopathies.

**Discussion** - All agents resulted in reduction of ICP, albeit transient in a number of occasions. A sustained reduction in ICP is desirable and could be achieved by modifying the modes and rates of administration, factors that need further investigation. Hypertonic saline appears to boost cerebral perfusion pressure, an important determinant of outcome in acute encephalopathies.

**Conclusion** - Hypertonic saline appears to achieve greater reduction in ICP than other osmotic agents. Oral glycerol seems to improve outcome among children with acute bacterial meningitis. However, the evidence is not sufficient to guide change of practice. More studies are needed to examine the safest and most efficacious concentrations of the various agents and the most effective routes and rates of administration of these agents.

**Key words** - Mannitol, hypertonic saline, urea, sorbitol, glycerol, albumin, encephalopathy, cerebral malaria, meningitis, encephalitis, metabolic, brain injuries, head injuries, coma, intracranial hypertension, child, pediatric and newborn infant.

**Introduction**

Raised intracranial pressure (ICP) is a recognized feature of both traumatic and non-traumatic acute encephalopathies. It has consistently been demonstrated to be an important determinant of outcome in children with central nervous system (CNS) infections and traumatic brain injuries (TBI). Raised ICP reduces cerebral perfusion pressure (CPP). CPP is the difference between the mean arterial pressure (MAP) and ICP (CPP = MAP – ICP). A reduction in CPP may lead to ischaemia if cerebro-vascular auto-regulation is impaired, with subsequent parenchymal damage. Raised ICP may also cause death by compressing the brainstem during trans-tentorial herniation. Therefore, management of raised ICP aims to reduce ICP, and optimize CPP and oxygen supply to the brain. Besides standard neuro-protective measures such as correction of hypoglycaemia and electrolyte imbalances, methods to achieve this include postural changes, temperature regulation, hyperventilation, sedation, drainage of cerebro-spinal fluid, operative decompression and osmotherapy.

Osmotherapy is widely used to control ICP, particularly in traumatic encephalopathies. It entails the use of pharmacologically inert substances that increase the osmotic pressure of plasma, promoting movement of water from interstitial space to vascular space. Osmotic agents include mannitol, urea, sorbitol, glycerol and hypertonic saline. Although these agents act mainly by reducing ICP via osmotic gradients, they may have other beneficial effects. Thus, mannitol has been shown to scavenge for reactive oxygen species. It may also reduce the viscosity of blood, improving its flow through the circulation. Hypertonic saline is known to enhance cardiac output and increase cerebral perfusion pressure.

Guidelines for use of osmotic agents have been developed from adult TBI studies. However, these have been adapted for children with minimal evidence obtained directly from children with TBI. Among children with non-traumatic encephalopathies, guidelines are virtually non-existent. The aim of the
present review was to determine the best available evidence of the effectiveness of various osmotic agents and their effect on resolution of coma and outcome (neurological sequelae and mortality) in children with acute encephalopathies.

**Objective**

The review questions examined were:

1. What is the effectiveness of osmotic agents in reducing intracranial pressure in children with acute encephalopathies?
2. What is the effect of osmotic agents on resolution of coma and outcome (neurological sequelae and mortality) in children with acute encephalopathies?

**Review method**

**Inclusion criteria**

**Types of studies**

We searched published and unpublished studies in the English and French languages between January 1966 and January 2008. For meta-analysis, we reviewed randomized controlled trials. In addition, we examined quasi- and non-randomized clinical trials, case control, cohort, and before and after studies, case series, and case reports. These studies are considered in the narrative summary.

**Types of participants**

We considered studies that included children aged between 0 and 16 years with acute traumatic and non-traumatic encephalopathies.

**Types of interventions**

We evaluated the use of osmotic agents in acute encephalopathies. Agents included in our search were mannitol, hypertonic saline, urea, sorbitol, albumin and glycerol.

**Types of outcome measures**

The primary outcome measure was reduction in ICP. Secondary outcome measures were resolution of coma and clinical outcome (neurological sequelae and death).

**Search Strategy**

We searched Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library and EMBASE. Other databases included were, Current Controlled Trials, The Trials Register of Promoting Health Interventions (TRoPHI), Australian Clinical Trials Registry (ACTR), Clinical Medicine Net Prints Collection, Bandolier Evidence Based Health Care, and The Center for Clinical Trials and Evidence-based Healthcare at Brown Medical School. The search databases for
unpublished studies and grey literature were Dissertation Abstracts International, WHO library, Agency for Healthcare Research and Quality, Grey Literature Report, National Library of Medicine, Theses Canada Portal, Proquest Digital Theses, Australasian Digital Theses Program and the British Library. The initial search analysed the text words contained in the title and abstract, and the index terms used to describe the articles. A second search that used all identified keywords and index terms, individually and in combinations, was applied. The reference list of all identified reports and articles were then searched for additional studies. Initial keywords used were mannitol, hypertonic saline, urea, sorbitol, glycerol, encephalopathy, cerebral malaria, meningitis, encephalitis, metabolic, brain injuries, head injuries, coma, intracranial hypertension, child, pediatric and newborn infant.

**Assessment of methodological quality**

The papers selected for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review. We used the standardized critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) Critical Appraisal tool (Appendix I). Any disagreements between the reviewers were resolved through discussion, or with a third reviewer.

**Data extraction**

Data was extracted using the standardised JBI data extraction tool (Appendix II).

**Data synthesis**

Quantitative studies were pooled in a statistical meta-analysis using the JBI-MAStARI. All data were entered twice and discrepancies resolved. Relative risk (for categorical data) and their 95% confidence intervals (95%CI) were calculated for analysis. Heterogeneity was assessed using the standard Chi-square test. Where statistical pooling was not possible, the findings are presented in a narrative form.

**Results**

We identified 20 studies that met our review criteria and critically appraised them using the JBI-MAStARI assessment tool, which excluded 10 studies (Appendix III). Four of these did not provide any data or information on the relationship between the interventions and the measured outcomes of interest\(^{12-15}\). Three studies included children and adults but data on children were not provided separately nor could we obtain this information from the authors\(^{16-18}\). Two other studies were excluded for other reasons\(^{19,20}\).

We included four randomized controlled trials (RCTs)\(^{21-24}\), one of which was a cross-over trial\(^{21}\), three prospective observational studies\(^{1,25,26}\), two retrospective studies\(^{27,28}\) and one case report\(^{29}\). Out of these, four studies involved patients with non-traumatic encephalopathies\(^{1,22,23,27}\). One clinical trial\(^{22}\) and one descriptive study\(^{1}\) were conducted in sub-Saharan Africa. Details of included studies are presented as Appendix IV.
Study focus

Intracranial Pressure

ICP was monitored in 7 studies; two RCTs\textsuperscript{21,24}, 4 observational studies\textsuperscript{1,25,26,28} and one case report\textsuperscript{29}. In one RCT, ringer’s lactate was compared to hypertonic saline for resuscitation of 32 children with traumatic brain injuries\textsuperscript{24}. Significantly more interventions for raised ICP were used in the Ringer’s lactate group compared to the hypertonic saline group (P <0.01)\textsuperscript{24}. However, no significant difference in the mean ICPs between these two groups was reported. In the other RCT, a crossover trial on 18 children with TBI, there was a significant reduction in ICP with use of hypertonic saline (P = 0.003)\textsuperscript{21}. A similar effect was not achieved with use of normal saline (P = 0.32). Hypertonic saline given as a continuous infusion in a study of 10 children with TBI achieved significant and sustained drop in ICP over 72 hours (P <0.01)\textsuperscript{25}. These were children with raised ICP that was refractory to other management including the use of bolus infusions of mannitol. In a prospective study of 23 children with cerebral malaria, a dose-response effect with use of boluses of mannitol was observed on moderately raised ICP (ICP>20mmHg, CPP<50mmHg) but not with severely raised ICP (ICP>40mmHg, CPP<40mmHg)\textsuperscript{1}. This effect was not sustained in a number of instances. In another study on 3 children with TBI, oral glycerol was shown to reduce ICP by at least 50% within the first half hour of administration and maximally after 60 minutes\textsuperscript{26}. This reduction was not maintained beyond 90 minutes. In the case report of two children with TBI, both hypertonic saline and mannitol showed a dose response relationship with ICP\textsuperscript{29}. However, Mannitol appeared to cause a reduction in CPP.

In overall, the five studies that investigated hypertonic saline\textsuperscript{21,24,25,28,29} demonstrated a dose-response effect on ICP irrespective of the saline concentrations.

Mortality

All the included studies reported on mortality. The four RCTs\textsuperscript{21-24} identified were heterogeneous in relation to the interventions used and could not be pooled for meta-analysis. In a multicentre trial on 654 children with bacterial meningitis, there was less mortality with use of glycerol compared to placebo (RR 0.64 95% CI 0.54, 0.76)\textsuperscript{23} and, with a combination of glycerol and dexamethasone compared to placebo (RR 0.79 95% CI 0.68, 0.92)\textsuperscript{23}. In another trial comparing the use of hypertonic saline and ringer’s lactate as resuscitative fluids in 32 children with TBI, the only 2 deaths observed were in children receiving ringer’s lactate\textsuperscript{24}. Among 156 children with cerebral malaria (CM), there was no observed difference in mortality in single bolus mannitol use compared to placebo (RR 0.81 95% CI 0.60, 1.09)\textsuperscript{22}. However, this study was not powered to detect difference in mortality. In a retrospective observation of children with non-traumatic encephalopathies, there was significantly less mortality with use of hypertonic saline compared to mannitol (RR 0.48 95% CI 0.34, 0.67)\textsuperscript{27}.

Neurological sequelae

Four studies reported on neurological sequelae\textsuperscript{1,23,25,28}. Only one of these, a clinical trial, had comparison groups\textsuperscript{23}. In this trial examining the use of glycerol and dexamethasone in 654 children with bacterial meningitis, severe neurological sequelae and profound hearing loss were examined as outcomes\textsuperscript{23}. When these two features were pooled, there were lower risks of severe neurological sequelae in the glycerol group compared to placebo (RR 0.58 95% CI 0.50, 0.67) and in the glycerol and dexamethasone combination (RR 0.55 95% CI 0.47, 0.65) compared to placebo. This lower risk
was similarly observed when severe neurological sequelae were examined alone. No significant differences were observed between the glycerol and the glycerol and dexamethasone combination.

**Resolution of Coma**

Only one study, a clinical trial of mannitol on children with CM, examined resolution of coma as an outcome measure\(^ {22}\). There was no difference between use of mannitol and placebo in coma resolution [median duration 6 (5-12) and 7 (3.5-12) hours respectively (p = 0.79)].

**Discussion**

We identified 4 RCTs, 1 of which was on children with non-traumatic encephalopathies. Each had a different combination of agents for comparison and could not be pooled for meta-analysis.

We also examined 1 cross over trial, 3 prospective observational studies, 2 retrospective observational studies and 1 case report.

We examined the dose response effect of the various interventions in studies where there was continuous monitoring of ICP. There was a dose response relationship with use of all the agents examined. However, like other physiological measurements, ICP is dynamic and a single measurement may be misleading. And thus, there is no apparent relationship between an initial single measurement of raised ICP and clinical outcome\(^ {1}\). The analysis of ICP measurements therefore consists of determining the duration of time that ICP is above a certain threshold\(^ {30}\). It is desirable that interventions result in sustained reductions in ICP. And so whilst all agents did exhibit a dose response effect, this was transient in a number of cases. Continuous infusions of hypertonic saline appeared to achieve sustained reduction in ICP. However, the advantage of different rates of administration can only be reliably investigated in clinical trials that specifically investigate the different modes and rates of administration of a particular intervention.

Hypertonic saline was shown to have a greater effect on ICP than either normal saline\(^ {21}\) or ringer’s lactate solutions\(^ {24}\). When compared to Mannitol, hypertonic saline maintained or improved CPP, an important determinant of neurological outcome\(^ {29}\). This effect is particularly important in acute encephalopathies associated with volume deficits as in TBI and CM. However, being a crystalloid, hypertonic saline may equilibrate freely throughout brain tissue in encephalopathies associated with impairment of the blood brain barrier such as meningitis, thus aggravating ICP.

There was a lower relative risk of death with hypertonic saline compared to mannitol\(^ {27}\), and with oral glycerol or a combination of oral glycerol and dexamethasone compared to placebo\(^ {23}\) (Appendix VI). In the latter study, there was no apparent advantage conferred by the use of steroids.

Neurological damage manifesting as neurological sequelae may be caused by impaired cerebral perfusion. Neurological sequelae were only reported in one comparative study. In this study, glycerol or glycerol and dexamethasone use was associated with fewer neurological sequelae compared to placebo\(^ {23}\) (Appendix VII). Studies to examine effects of osmotic agents on neurological outcome would require larger samples sizes and longer durations of follow up than those of the studies we examined.

We restricted our search to studies that were published in the English and French languages after 1966, potentially missing out on a number of studies in other languages. However, it is unlikely that a search of literature before 1966 could have yielded adequately reported studies on children. In three studies that we included, the osmotic agents were examined for use as resuscitative fluids, not for
treatment of ICP. Nevertheless, these studies did provide data on the outcomes of interest and inadvertently revealed a more effective mode of administration of osmotic agents, supporting continuous rather than bolus infusions. We have included one study that had a mixed population of children and adults\textsuperscript{26}. In this study, some of the data on children is provided separately. Another study investigated children with a varied aetiology of acute encephalopathies\textsuperscript{31}. Even so, the pathophysiology of raised ICP and the mode of action of the agents are likely to be the same in the children irrespective of aetiology.

**Conclusion**

The evidence appears to favor the use of oral glycerol in children with acute bacterial meningitis and the use of hypertonic saline in acute traumatic and non-traumatic encephalopathies. The evidence presented is not sufficient to provide guidelines. Further clinical trials are needed to examine the safest and most efficacious concentrations of the various agents, particularly hypertonic saline. Such studies will also guide on the appropriate routes of administrations and the optimum rates of administration of these agents. Multicentre trials may be necessary to achieve adequate sample sizes.

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**Conflicts of Interest**

There are no conflicts of interest.

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Appendix I: JBI MASTARI Critical Appraisal Tool

JBI critical appraisal checklist for Randomized/Pseudo-randomized controlled trials

Primary/Secondary/Final

Criteria

1) Was the assignment to treatment groups truly random? Y/N
2) Were participants blinded to treatment allocation? Y/N
3) Was allocation to treatment groups concealed from the allocator? Y/N
4) Were the outcomes of people who withdrew described and included in the analysis? Y/N
5) Were those assessing outcomes blind to the treatment allocation? Y/N
6) Were the control and treatment groups comparable at entry? Y/N
7) Were groups treated identically other than for the named interventions? Y/N
8) Were outcomes measured in the same way for all groups? Y/N
9) Were outcomes measured in a reliable way? Y/N
10) Was appropriate statistical analysis used? Y/N

Include? Y/N

Reason for not including

JBI critical appraisal checklist for Descriptive/ Case Series studies

Primary/Secondary/Final

Criteria

1) Was study based on a random or pseudo-random sample? Y/N
2) Were the criteria for inclusion in the sample clearly defined? Y/N
3) Were confounding factors identified and strategies to deal with them stated? Y/N
4) Were outcomes assessed using objective criteria? Y/N
5) If comparisons are being made, was there a sufficient description of the groups? Y/N
6) Was follow up carried out over a sufficient time period? Y/N
7) Were the outcomes of people who withdrew described and included in the analysis? Y/N
8) Were outcomes measured in a reliable way? Y/N
9) Was appropriate statistical analysis used? Y/N

Include? Y/N

Reason for not including______________________________________________________

**JBI critical appraisal checklist for comparable cohort/case control study**

*Primary/Secondary/Final*

Criteria

1) Is sample representative of patients in the population as a whole? Y/N
2) Are the patients at a similar point in the course of their condition/illness? Y/N
3) Has bias been minimized in relation to selection of cases and of controls? Y/N
4) Are confounding factors identified and strategies to deal with them stated? Y/N
5) Are outcomes assessed using objective criteria? Y/N
6) Was follow up carried out over a sufficient time period? Y/N
7) Were the outcomes of people who withdrew described and included in the analysis? Y/N
8) Were outcomes measured in a reliable way? Y/N
9) Was appropriate statistical analysis used? Y/N

Include? Y/N

Reason for not including______________________________________________________
Appendix II: Standardized JBI Data Extraction Tool

Extraction details: ____________________________________________________________

Study information
Method: _________________________________________________________________
Setting: ________________________________________________________________
Participants: ______________________________________________________________
Number of Participants:  
Group A: _______________________
Group B: _______________________

Interventions
Intervention A: __________________________________
Intervention B: __________________________________

Authors’ conclusion: ______________________________________________________

Reviewer’s comments: ____________________________________________________

Complete: Y/N
Appendix III: Reasons for excluding studies

Cruz J, Nakayama P, Imamura JH, Rosenfeld KG, de Souza HS, Giorgetti GV. Cerebral extraction of oxygen and intracranial hypertension in severe, acute, pediatric brain trauma: preliminary novel management strategies. *Neurosurgery* 2002;50(4):774-9; discussion 779-80. **Reason for exclusion:** The use of the intervention, mannitol, was not clearly evaluated and the study does not demonstrate the relationship between mannitol use and outcome.

James HE. Methodology for the control of intracranial pressure with hypertonic mannitol. *Acta Neurochir (Wien)* 1980;51(3-4):161-72. **Reason for exclusion:** The study provides combined results for adults and children.

James HE, Langfitt TW, Kumar VS, Ghostine SY. Treatment of intracranial hypertension. Analysis of 105 consecutive, continuous recordings of intracranial pressure. *Acta Neurochir (Wien)* 1977;36(3-4):189-200. **Reason for exclusion:** The study provides combined results for adults and children.

Kingston ME. Experience with urea in invert sugar for the treatment of cerebral malaria. *J Trop Med Hyg* 1971;74(11):249-52. **Reason for exclusion:** There is little information on the characteristics of the participants. There is no data provided on the effect of the intervention, urea, on ICP or outcome.

MacDonald JT, Uden DL. Intravenous glycerol and mannitol therapy in children with intracranial hypertension. *Neurology* 1982;32(4):437-40. **Reason for exclusion:** Reason for selective data presentation not given and administration of both treatments not clearly described.

Marshall LF, RW SM, Rauscher LA, Shapiro HM. Mannitol dose requirements in brain-injured patients. *J Neurosurg* 1978;48(2):169-72. **Reason for exclusion:** Age of subjects is not given and statistical methods used not clear.

Mickell JJ, Reigel DH, Cook DR, Binda RE, Safar P. Intracranial pressure: monitoring and normalization therapy in children. *Pediatrics* 1977;59(4):606-13. **Reason for exclusion:** The relationship between the intervention and ICP or outcome is not described.

Prabhakaran P, Reddy AT, Oakes WJ, King WD, Winkler MK, Givens TG. A pilot trial comparing cerebral perfusion pressure-targeted therapy to intracranial pressure-targeted therapy in children with severe traumatic brain injury. *J Neurosurg* 2004;100(5 Suppl Pediatrics):454-9. **Reason for exclusion:** The paper did not report on effect of the intervention, mannitol, on ICP or outcome.

Procaccio F, Menasce G, Sacchi L, Boselli L. Effects of thiopentone and mannitol on cerebral perfusion pressure and E.E.G. in head injured patients with intracranial hypertension. *Agressologie* 1991;32(8-9 Spec No):381-5. **Reason for exclusion:** The study included a heterogeneous age group of patients that is not comparable and in whom standard treatment was not provided to all.

Vialet R, Albanese J, Thomachot L, et al. Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. *Crit Care Med* 2003;31(6):1683-7. **Reason for exclusion:** The study provides combined results for adults and children.
## Appendix IV: Assessment of Included Studies

| Study | Fisher 1992<sup>21</sup> | Namutangula 2007<sup>22</sup> | Peltola 2007<sup>23</sup> | Simma 1998<sup>24</sup> |
|-------|-----------------|-----------------|-----------------|-----------------|
| Was the assignment to treatment groups truly random? | Y | Y | Y | Y |
| Were participants blinded to treatment allocation? | N | Y | Y | Y |
| Was allocation to treatment groups concealed from the allocator? | U | Y | Y | N |
| Were the outcomes of people who withdrew described and included in the analysis? | Y | Y | Y | Y |
| Were those assessing outcomes blind to the treatment allocation? | U | Y | Y | N |
| Were the control and treatment groups comparable at entry? | N | Y | Y | Y |
| Were the groups treated identically other than for the named interventions? | Y | Y | Y | Y |
| Were outcomes measured in the same way for all groups? | Y | Y | Y | Y |
| Were outcomes measured in a reliable way? | Y | Y | Y | Y |
| Was appropriate statistical analysis used? | Y | Y | Y | Y |

### Assessment of Cohort/Case control study

| Study | Yildizdas 2006<sup>27</sup> |
|-------|-----------------|
| Is sample representative of patients in the populations as a whole? | Y |
| Are the patients at a similar point in the course of their condition/illness? | Y |
| Has bias been minimized in relation to selection of cases and of controls? | U |
| Are confounding factors identified and strategies to deal with them stated? | N |
| Are outcomes assessed using objective criteria? | Y |
| Was follow up carried out over a sufficient time period? | Y |
| Were the outcomes of people who withdrew described and included in the analysis? | Y |
| Were outcomes measured in a reliable way? | Y |
| Was appropriate statistical analysis used? | Y |
### Assessment of descriptive and case series studies

| Study                                      | Berger 2002<sup>29</sup> | Peterson 2000<sup>28</sup> | Khanna 2000<sup>25</sup> | Newton 1997<sup>1</sup> | Wald 1982<sup>26</sup> |
|--------------------------------------------|---------------------------|-----------------------------|--------------------------|--------------------------|--------------------------|
| Was study based on a random or pseudo-random sample? | N                          | N                           | N                        | N                        | N                        |
| Were the criteria for inclusion in the sample clearly defined? | Y                          | Y                           | Y                        | Y                        | N                        |
| Were confounding factors identified and strategies to deal with them stated? | N                          | N                           | U                        | U                        | U                        |
| Were outcomes assessed using objective criteria? | Y                          | Y                           | Y                        | Y                        | Y                        |
| If comparisons were being made, were there sufficient descriptions of the groups? | Y                          | Y                           | Y                        | Y                        | Y                        |
| Was follow up carried out over a sufficient time period? | Y                          | Y                           | Y                        | Y                        | Y                        |
| Were the outcomes of people who withdrew described and included in the analysis? | Y                          | Y                           | Y                        | Y                        | Y                        |
| Were outcomes measures in a reliable way? | Y                          | Y                           | Y                        | Y                        | Y                        |
| Was appropriate statistical analysis used? | Y                          | Y                           | Y                        | Y                        | Y                        |
| Study Design | Study population | Settings | Intervention | Outcome | Author’s conclusions | Reviewer’s comments |
|-------------|-----------------|----------|--------------|---------|----------------------|---------------------|
| *Peltola 2007*<sup>23</sup> | Multicentre RCT | Children with ABM | Multiple centres, South America | (1) Oral glycerol 1.5g/Kg QID <br>(n=166) <br> (2) Oral glycerol 1.5g/Kg & Dexamethasone 0.15mg/Kg QID <br>(n=159) <br> (3) Placebo <br>(n=163) <br> (4) Dexamethasone <br>(n=166) | Death <br>1 = 17 <br>2 = 20 <br>3 = 26 <br>4 = 23 <br>(p = 0.383, determined by the x<sup>2</sup> tests between the groups) <br>Severe Neurological sequelae <br>1 = 7 (P = 0.01) <br>2 = 8 (P = 0.03) <br>3 = 19 <br>4 = 10 <br>(p = 0.022, determined by the x<sup>2</sup> tests between the groups) <br>Profound hearing loss <br>1 = 12 <br>2 = 9 <br>3 = 12 <br>4 = 10 <br>(p = 0.879, determined by the x<sup>2</sup> tests between the 4 groups) | Neurological sequelae alone and combined death and neurological sequelae occurred with significantly less frequency in the Glycerol and Glycerol and Dexamethasone groups compared to the placebo and Dexamethasone groups. <br>Hearing loss occurred with similar frequency in the 4 groups. <br>The use of antimicrobials and timing of their administration w.r.t. initiation of the treatment did not change the results. | The study is comprehensive and well designed to measure the effects of the agents. It demonstrates an obvious advantage in the use of glycerol alone or glycerol with Dexamethasone against placebo in reducing severe neurological sequelae. However, assessment of neurological sequelae at discharge was not enough to evaluate overall neurological outcome and should ideally have been repeated a few months after discharge. Withdrawals are described but are not included in per-protocol analysis. There were some protocol differences between the different sites. Dexamethasone use has not been examined in our review. |
| *Namutanga 2007*<sup>22</sup> | RCT | Children with CM | Uganda | Mannitol 1g/Kg <br>(n = 76) <br> Placebo <br>(n = 80) | Death | Mannitol does not significantly reduce time taken to regain consciousness, sit unsupported or mortality. | The sample size was too small to determine effect of mannitol on mortality. ICP is not measured and as such, it is not determined if all the patients warranted treatment with mannitol. Because of this, the potential effect of mannitol is diluted. Mannitol is administered as an initial single dose. ICP is dynamic and mannitol itself has a limited duration of action. The single dose |
| Study          | Design Type                  | Participants | Country | Treatment | Death | Use of hypertonic saline for resuscitation and fluid management during the first 3 days after severe head injury is associated with lower intracranial pressure, higher cerebral perfusion and fewer adverse events compared to Ringer's Lactate. Children who received Hypertonic saline remained comatose for shorter durations and had less mortality. |
|---------------|------------------------------|--------------|---------|-----------|-------|-------------------------------------------------|
| Simma 1998    | RCT                          | TBI children | Switzerland | Hypertonic saline (HS) (n = 15) | Death | Greater need for other interventions to keep ICP at ≤ 15mmHg in RL patients compared to the HS patients (p < 0.01) |
|               |                              | N = 32       |         | Ringer's Lactate (RL) (n = 17) |       |                                                  |
| Fisher 1992   | Double blind crossover trial | TBI children | USA     | 3% HS     |       | Acute hypernatremia achieved with use of 3% HS is associated with decreased ICP in pediatric patients over a short period. |
|               |                              | N = 18       |         | 0.9% Saline (Crossover study) |       |                                                  |

**Data from Simma 1998**

- **RCT**
- **TBI children**
- **Switzerland**
- **Hypertonic saline (HS)** (n = 15)
- **Death**
  - HS = 0
  - RL = 2
- **Greater need for other interventions to keep ICP at ≤ 15mmHg in RL patients compared to the HS patients (p < 0.01)**

**Data from Fisher 1992**

- **Double blind crossover trial**
- **TBI children**
- **USA**
- **3% HS**
- **0.9% Saline (Crossover study)**
- **Change in Intracranial pressure**
  - 3% HS Initial ICP = 19.9mmHg
  - Average ICP = 15.8mmHg (P = 0.003)
- **0.9% Saline**
  - Initial ICP = 19.3 mmHg
  - Average ICP = 20.0 mmHg (P = 0.32)

**Note:** In this study, hypertonic saline is being examined as a resuscitative fluid rather than a direct intervention for raised intracranial pressure. In cases where ICP was raised, the patients received specific therapy which in some cases included Mannitol. Even so, they are still able to demonstrate lower incidence of raised ICP and death in children who received hypertonic saline compared to those who received ringers lactate.

There is an evident dose response effect with use of hypertonic saline (3%) but the duration of observation is too short to examine for sustained response. A similar effect on ICP is not seen with 0.9% saline and in 10 instances, the ICP rose warranting other interventions. Standard deviations are not provided for the means of ICP after interventions of either agent; this would have facilitated comparisons. However, 3% saline appears to be more effective than 0.9% saline in managing raised ICP.
| Study | Design | Population | Intervention | Outcome |
|-------|--------|------------|--------------|---------|
| Khanna 2000<sup>25</sup> | Prospective observational study | TBI Children with refractory RICP | 3% HS infusion | Change in intracranial pressure: There was a decrease in ICP between time 0 and at 6, 12, 24, 48 and 72 hours after initiation of therapy (p < 0.01). There was a decrease in ICP spike frequency at 6, 12, 24, 48 and 72 hours after start of therapy (p < 0.01). Hypertonic saline effectively controls intracranial hypertension resistant to conventional therapy. There is a statistically significant relationship between serum sodium and ICP. The clinical outcome in these patients is impressive as a result of hypertonic saline use. Only one child died and the authors attribute this to late presentation. |
| Newton 1997<sup>26</sup> | Prospective observational study | Children with CM and moderate or severe ICP | Mannitol 0.5-1g/Kg | Mannitol reduced ICP in all instances. This change was not sustained in a number of occasions and was not examined systematically for significance. Mannitol was effective in children with moderate ICP but not in those with severe ICP. It was not clear if Mannitol influenced outcome. |
| Wald 1982<sup>25</sup> | Prospective Observational Study | TBI children with ICP>300mm of H<sub>2</sub>O | Glycerol 0.5-1g/Kg every 3-4 hrs | Change in ICP: Mean ICP reduced in the children after Glycerol infusion with lowest ICP being achieved at 60 minutes after which it appears to gradually rise (as shown by the graph). Glycerol use resulted in reduction of ICP independent of initial level of pressure. Further conclusions cannot be drawn as all patients (adults and children) are grouped together and data specific to children is not provided. |
| Yildizdas 2006<sup>27</sup> | Retrospective study | Children with non-traumatic encephalopathies | I - Mannitol 0.5g/Kg (n = 22) II - HS (n = 25) III - Mannitol (n = 22) | Deaths: I = 11 II = 6 III = 3 (P = 0.003) Resolution of coma (mean): I = 123 hrs II = 88.6 hrs III = 87.5 hrs The administration of HS is safer and more effective than mannitol. Groups II (HS only) and III (HS and Mannitol) showed better results in relation to duration of coma and mortality. The authors acknowledge the lack of ICP monitoring! The combined group was categorized into 2; those who received both agents (A) and... |
| Study          | Design       | Population                              | Location | Osmotic Agents | Change in ICP | Measurement |
|---------------|-------------|-----------------------------------------|----------|----------------|---------------|-------------|
| Peterson 2000 | Retrospective Observations | TBI children, ICP>20mmHg | USA       | 3% HS infusion | No quantitative data is provided on this | Continuous infusion of HS was efficacious and safe for use in managing raised ICP in paediatric TBI. |
| Berger 2002   | Case report | 11 & 12 yr old children with TBI       | Germany  | 20% HS         | Change in ICP | HS appeared to reduce post-traumatic increased ICP and improve cerebral perfusion pressure more effectively than comparable amounts of mannitol. |
|               |             |                                        |          | 20% Mannitol    |               | A dose response effect on ICP with use of both osmotic agents is demonstrated but mannitol appears to cause a reduction in cerebral perfusion pressure. |

- 0.5g/Kg and HS (n = 20) (P = 0.004) measurement as a disadvantage in their study and conclude that proper timing of treatment requires ICP monitoring.

- Those who received hypertonic saline after stopping mannitol (B). The outcomes were not similarly grouped. For the purpose of our review, we have excluded this group.

- It is also not clear whether treatment allocation was done randomly or was period specific.

- The study includes young infants, a group that needs to be analysed separately because they have an immature nervous system and patent fontanels which partly protects them from the effect of raised intracranial pressure. This also has a bearing on scoring for coma which is one of the outcomes examined.
Appendix VI: Relative risk for death

Relative risks for death

Mortality

Glycerol vs DexGlycerol
Placebo vs DexGlycerol
Placebo vs Glycerol
Placebo vs Mannitol
Mannitol vs HS

*Dex = Dexamethasone
Appendix VII – Relative risk for neurological sequelae

Relative risks for neurological sequelae

*Dex = Dexamethasone