Review of the role of mannitol in the therapy of children

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† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.
Introduction

At its meeting in October 2007, the WHO Subcommittee of the Expert Committee for the Selection and Use of Essential Medicines requested that the role of Mannitol in children be reviewed in light of potentially newer and more effective medicines for the next meeting of the Expert Committee [1]. A literature review was, therefore, undertaken to determine existing evidence for the comparative safety and efficacy for the use of Mannitol in children.

Background

Mannitol, an osmotic agent, is a naturally occurring sugar alcohol that can be used orally or intravenously. Oral Mannitol is used for bowel preparation and intravenous Mannitol is used to induce diuresis in clinical situations, such as cerebral oedema and acute renal failure [2]. As an osmotic diuretic, Mannitol is most commonly used in the intensive care unit [3]. Mannitol is currently recommended for the treatment of cerebral oedema and raised intraocular pressure as well as for the assessment of renal function [4].

To identify current paediatric guidelines and recommendations for Mannitol, several resources were reviewed including: WHO publications, paediatric and pharmacology text books, the Brain Trauma Foundation web site and publications, WHO regional databases, FDA website, BNF, Australian handbook, and international pharmacopoeias. (See table 1).

Table 1: available guidelines for Mannitol

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<tr>
<td>Paediatric specific guidelines</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<td>No</td>
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<tr>
<td>Indications</td>
<td>Cerebral oedema, raised intraocular pressure, assessment of renal function</td>
<td>Cerebral oedema, raised intraocular pressure</td>
<td>Raised intracranial pressure</td>
<td>Management of severe traumatic brain injury</td>
<td>Acute renal failure, cerebral oedema, elevated intraocular pressure, urinary excretion of toxins, urologic irrigation</td>
<td>Acute renal failure, cerebral oedema, elevated intraocular pressure, nonspecific toxicity, haemolysis prophylaxis</td>
</tr>
<tr>
<td>Formulations</td>
<td>Injectable (IV) solutions 10% &amp; 20%</td>
<td>Injectable (IV) solutions 10% &amp; 20%</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Injectable (IV) solutions 10%, 15%, 20% &amp; 25%</td>
<td>Injectable (IV) solutions 5%, 10%, 15%, 20% &amp; 25%</td>
</tr>
<tr>
<td>Dose</td>
<td>To assess</td>
<td>In cerebral</td>
<td>Not stated</td>
<td>0.25-1 g/kg</td>
<td>0.2 g/kg</td>
<td>0.25-2 g/kg</td>
</tr>
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</table>

† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.
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<tbody>
<tr>
<td>renal function: Child all ages, 200 mg/kg</td>
<td>Cerebral oedema: Child 1 month-12 years old 0.25-1.5 g/kg</td>
<td>oedema: Neonate 0.5-1 g/kg Child 1 month-18 years old 0.5-1.5 g/kg In peripheral oedema and ascitis: Child 1 month-18 years old 1-2 g/kg</td>
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Mannitol is currently listed in the WHO Model List of Essential Medicines on the complementary list because the administration of Mannitol needs special diagnostic and clinical skills and training as well as specific treatment facilities and medical devices such as a syringe with in-line filter. Continual assessment of neurologic status, including ICP monitoring, is required to assess the need for administration of hyperosmolar agents such as Mannitol. Renal function, daily fluid I & O, serum electrolytes, and serum and urine osmolality should be monitored while mannitol is being administered; for treatment of elevated intracranial pressure, serum osmolality should be maintained 310 to <320 mOsM/kg [5]. For systemic effect, Mannitol must be given parenterally. Mannitol has to be administered as intermittent bolus doses via central venous access. It has the potential to crystallize and if crystals are present, they have to be dissolved by warming infusion fluids and through a 5-micron in-line filter [6].

**Detailed specification of Mannitol active pharmaceutical ingredients, dosage forms & strength, publically available formulations, FDA registered formulations**

**Active ingredient:** Mannitol

**Forms and strength available** [7]:

- Mannitol: Injection - 5 % (5mg/100ml), 10 % (10mg/100ml), 15 % (15 mg/100ml), 20 % (20mg/100ml), 25 % (12.5mg/50ml)
- Osmitrol: injection 5% 10%, 15%, 20%, 25%

**Pharmacokinetics** [8]: Mannitol is poorly absorbed by the GI tract, and when administered orally it causes osmotic diarrhea. For systemic effect, mannitol must be given parenterally. Mannitol is not metabolized and is excreted by glomerular filtration within 30-60 minutes, without any important tubular reabsorption or secretion.

† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.
Pharmacodynamics* [8]: Osmotic diuretics have their major effect in the proximal tubule and the descending limb of Henle's loop. Through osmotic effects, they also oppose the action of ADH in the collecting tubule. The presence of a nonreabsorbable solute such as mannitol prevents the normal absorption of water by interposing a countervailing osmotic force. As a result, urine volume increases. The increase in urine flow rate decreases the contact time between fluid and the tubular epithelium, thus reducing $\text{Na}^+$ as well as water reabsorption. The resulting natriuresis is of lesser magnitude than the water diuresis, leading eventually to excessive water loss and hypernatremia.

*No English language articles focusing on the pharmacokinetic and pharmacodynamics of Mannitol in children were identified.

Public Health Burden

Mannitol is currently used in the management of elevated Intracranial Pressure (ICP), also known as intracranial hypertension or cerebral oedema (†).

Intracranial hypertension can happen due to several reasons: 1) intracranial (primary): CNS infection, trauma, brain tumour, intracranial bleeding, status epilepticus, and others (ischemic stroke, hydrocephalous, idiopathic or benign intracranial hypertension). 2) Extracranial (secondary): hypoxic ischemic injury, metabolic, drugs, and others (hypertensive encephalopathy). 3) Postoperative: hematoma, cerebral oedema, vasodilatation, CSF obstruction [9]. Elevated ICP is a medical emergency and demands aggressive and immediate attention. After surgical evacuation of space occupying lesions, the most widely used agent to reduce ICP is mannitol. A number of studies have failed to document any effectiveness of mannitol in reducing mortality in head injury. However, the effectiveness of mannitol for head injury patients in critical conditions is considered to be well established without the need for randomized controlled trials [10]. Almost 83% of centers in United States use osmotic diuretics in more than 50% of patients with severe head injury [11]. A study in the United Kingdom showed that all the neurological centres use mannitol for the treatment of raised ICP [12]. It was not clear if children were being treated at these centres or not. Elevated ICP is a common and serious consequence of head injury world wide. An estimated 1.7 million people sustain a traumatic brain injury (TBI) annually, of these 52,000 die, 275,000 are hospitalized, and 1.365 million, nearly 80%, are treated and discharged from an emergency department. TBI is a contributing factor to a third (30.5%) of all injury-related deaths in the United States. Children aged 0 to 4 years, older adolescents aged 15 to 19 years, and adults aged 65 years and older are most likely to sustain a TBI. Almost half a million (473,947) emergency department visits for TBI are made annually by children aged 0 to 14 years [13]. Another major cause of elevated of ICP in children is diabetic ketoacidosis (DKA). Cerebral oedema is a devastating complication of DKA in children and it occurs in 25-40% of children with newly diagnosed type 1 diabetes mellitus [14]. Cerebral oedema is the most common complication of DKA with a mortality rate of 20-90% [15]. DKA has been associated with 83% of deaths in children with diabetes [16]. TBI can cause a wide range of functional short- or long-term changes affecting thinking, sensation, language, or emotions [13]. The financial impact of unintentional childhood injury has an estimated cost of $347 billion each year, including $17 billion for medical cost, $72 billion in future work lost, and $257 billion in quality of life lost [17]. There is a lack of global statistics on the incidence of traumatic brain injury in children; however, there are some local statistics available. For instance, traumatic injuries account for 40% of deaths in children >1 year old in the US, and head injury is the leading cause of death. More than 30% of all admissions to a PICU are due to serious head injury [18]. Traumatic injuries are reported as the leading cause of death and a major cause of long term disabilities in children > 1 year old in the UK. In 1997, 338 deaths in children <15 years old in England and Wales were due to head injury [19]. Each year traumatic brain injury affects 3/1000 Americans. It is the leading cause of mortality and morbidity after a trauma and accounts for 56000 deaths/year and its economic burden is $33000/person [20].

† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.
Recommendations for the management of elevated ICP include sedation, osmotic diuretics, paralysis, cerebrospinal fluid drainage, and hyperventilation [21]. In 2005, Knap et al reported that administering mannitol has become the corner stone in the treatment of patients with severe head injury and elevated ICP particularly in the acute management phase. Multiple studies provide data on the mechanism by which mannitol works; however, there have been no controlled clinical trials against placebo or other hyperosmolar agents in pediatric patients nor are there data to validate different regimens of mannitol administration. Mannitol side effects include development of acute renal failure and rebound cerebral edema. Data from adult studies indicate a risk for development of acute tubular necrosis and renal failure because mannitol is excreted unchanged in urine [22]. Osmotic diuretics such as Mannitol or 3% hypertonic normal saline are often used to treat intracranial hypertension. The osmotic effects on the cells and interstitium of the brain prolong the reduction in ICP [23].

Current paediatric specific guidelines recommend a dose of 0.25-1.5 g/kg of Mannitol for the management of intracranial hypertension in children (see table 1a).

Table 2: Indications and dose regimens for Mannitol in children

<table>
<thead>
<tr>
<th>Indication/s</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Cerebral oedema, raised intraocular pressure, assessment of renal function ††</td>
<td>Cerebral oedema: Child 1 month-12 years old 0.25-1.5 g/kg To assess renal function: Child all ages. 200 mg/kg</td>
</tr>
<tr>
<td>Cerebral oedema, raised intraocular pressure†††</td>
<td>In cerebral oedema: Neonate 0.5-1 g/kg(2.5-5 mL/kg of 20% solution) repeated if necessary 1-2 times after 4-8 hours Child 1 month-18 years 0.5-1.5g/kg( 2.5-7.5 mL/kg of 20% solution) repeated if necessary 1-2 times In peripheral oedema and ascites: Child 1 month- 18 years 1-2 g/kg IV infusion over 2-6 hours</td>
</tr>
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†† WHO model formulary for children 2008  
††† BNF for children 2009

Cerebral oedema is a devastating complication of DKA in children and it occurs in 25-40% of children with newly diagnosed type 1 diabetes mellitus [14].

Mannitol has also been used in other clinical situations such as mannitol challenge test in asthma and as a therapeutic measure in cystic fibrosis. According to Medline Plus, about 20 million people in the US have asthma and 9 million of them are children. Children have smaller airways than adults which makes asthma especially serious for them [24]. About 17 million Americans suffer from asthma. The cost of illness related to asthma is about $6.2 billion per year in the US. About 1.81 million asthmatic patients require treatment in the emergency department and half a million need hospitalization. Children younger than 18 years account for 47% of emergency department visits and 34.6% of the hospitalization due to exacerbation of asthma. Asthma accounts for more school absences than any other chronic condition [25].

According to CDC.gov, after Sickle Cell Disease, Cystic Fibrosis is the second most common life-shortening child onset inherited disorder in the U.S. Each year 1000 new cases are diagnosed. CF is
a chronically debilitating disease that affects the respiratory, gastrointestinal, and reproductive systems. It is the most prevalent, life-shortening, hereditary disease among white children, with an incidence ranging from 171,700 to 1/6,500. In 1995, 20,000-25,000 people in the US had CF. CF pulmonary disease is associated with viscous, purulent secretions. The main aims in the treatment of CF are: correction of pancreatic insufficiency, treatment of obstructive lung disease by clearance of lower airway secretions, treatment of secondary pulmonary infections with antibiotics and adjunct anti-inflammatory, bronchodilatory, and mucoactive agents. According to Cystic Fibrosis Foundation, CF is an inherited chronic disease that affects the lungs and digestive system of about 30,000 children and adults in the United States (70,000 worldwide). A defective gene and its protein product cause the body to produce unusually thick, sticky mucus that: clogs the lungs and leads to life-threatening lung infections; and obstructs the pancreas and stops natural enzymes from helping the body break down and absorb food[26].

**Search methods for identification of safety and efficacy data**

An online database search for articles published from 1950 to present was conducted using search terms mannitol and children (see appendix 1 for detailed list of search terms). The relevant articles were studied and summarized in combination with the other resources, such as paediatrics and pharmacology textbooks, communications with first authors and experts, international pharmacopoeias, and direct communication with FDA and national Clearinghouse Guidelines. The following databases were searched:

- **Electronic searches**
  1. Cochrane library
  2. Pubmed
  3. Embase

- **Searching other resources:** multiple sources were used wherever possible to validate the data.

**Inclusion criteria:**

- English language articles
- Human subjects
- Types of studies:
  1. Systematic reviews
  2. Randomized controlled trials which subjects were assigned to treatment or control group (placebo-controlled or different drug from Mannitol) on the basis of random allocation.
  3. Reviews
  4. Observational studies
- Types of participants:
  Children between 0-12 years old
- Types of interventions: the treatment group received Mannitol at any dose for any duration at any time

**Exclusion criteria:**

- non English language articles
- animal studies
- Studies not targeting paediatric population
- Studies including paediatric populations, but paediatric specific data not reported separately
- Studies without clear specification of intervention or dose
- Individual case reports

† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.
Results
See appendix 1 and 2 for Cochrane library, Pubmed, and Embase search strategies, number of citations found, and the flow charts for selecting the included articles.

Description of the included studies (see appendix 3 for data extraction tables)

Systematic reviews

No Cochrane Systematic reviews were identified that reported outcomes specifically for children ≤12 years. Three other systematic reviews that evaluated the use of mannitol in children met the inclusion criteria for this review.

William McGuire. 2007. Systematic review: Perinatal Asphyxia. (See Appendix 3, Table 1)
This systematic review addressed the clinical question "what are the effects of interventions in term or near-term newborns with perinatal asphyxia?" The review presented information relating to the effectiveness and safety of the following interventions: anticonvulsants, antioxidants, calcium channel blockers, corticosteroids, fluid restriction, head and/or whole body hypothermia, hyperbaric oxygen treatment, hyperventilation, linotrope support, magnesium sulphate, mannitol, opiate antagonists, and resuscitation.

In total, the review included 7 RTCs and 2 case series. Of these, only one small RCT (n=25, term neonates) included mannitol. This was a comparative study of mannitol vs. no drug treatment. A single dose of mannitol (1 g/kg) was administered. No side effects were reported. The results showed that a single dose of mannitol was no more effective at reducing mortality rates in neonates with asphyxia compared with no drug treatment (AR 4/12 [33%] with mannitol vs. 4/13 [31%] with no drug treatment). No data were available on long term neurodevelopmental outcomes.

Overall, the systematic review concluded that there is currently insufficient evidence to determine whether the effectiveness and safety of the following interventions: anticonvulsants, antioxidants, calcium channel blockers, corticosteroids, fluid restriction, head and/or whole body hypothermia, hyperbaric oxygen treatment, hyperventilation, linotrope support, magnesium sulphate, mannitol, or opiate antagonists are beneficial in infants with perinatal asphyxia, and resuscitation. Based on the current available evidence, it is not possible to determine if mannitol has a role in the treatment of perinatal asphyxia.

Andrew Whitelaw. 2000. Systematic Review: Systematic review of therapy after hypoxic-ischemic brain injury in the perinatal period. (See Appendix 3, Table 2)
The objective of this systematic review was to identify and evaluate controlled trials of interventions for term infants developing hypoxic-ischemic encephalopathy. In total, the review included 7 RCTs, 4 observational studies, 1 uncontrolled study, 6 retrospective study, and 2 case series. Only 1 case series report (infants), 1 observational study (infants), and 1 uncontrolled study (full term infants), total n= 258 included Mannitol as an intervention. All 3 studies used 20% mannitol 1 g/kg IV. The uncontrolled study and the observational study did not state any side effects.

The uncontrolled study reported improvement of prognosis; the observational study reported a reduction of ICP and elevation of cerebral perfusion 60 minutes after starting the infusion and concluded that mannitol infusion seemed of value in treating raised ICP associated with cerebral oedema and its cautious use was recommended if ICP monitoring is available. However, the

† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.
findings from these 2 studies should be interpreted with caution due to the lack of randomization of the study participants. Based on the findings of this systematic review, no definite recommendation regarding the use of mannitol in hypoxic-ischemic brain injury in the perinatal period can be made. Use of mannitol needs to be paired with ICP monitoring. If such monitoring is not available its use should not be recommended.

Regarding the results for the other interventions included in this systematic review, it was noted that there were methodological problems with all of the five RCTs concerning prophylactic use of anticonvulsants for neonates with HIE. Moreover, the meta-analysis of barbiturate prophylaxis showed no significant effect on death or disability. One randomized trial of allopurinol showed short-term benefits, but was too small to test death or disability. One small randomized trial of hypothermia found no adverse effects, but was too small to examine death or disability. No adequate trials of dexamethasone, calcium channel blockers, magnesium sulphate, or naloxone have yet been completed, but pilot studies in infants have shown that magnesium sulphate and calcium channel blockers can cause hypotension in babies.

Samson Gwer. 2010. Systematic Review: The role for osmotic agents in children with acute encephalopathies: a systematic review. (See Appendix 3, Table 3)
The objective of this systematic review was to determine the current evidence of the effectiveness of osmotic agents and their effect on resolution of coma and outcomes in children with acute encephalopathy due to cerebral oedema, elevated ICP, or cerebral oedema of infection, anoxic, hemorrhagic, and metabolic origin. The systematic review included 4 RCTs, 3 prospective observational studies, 2 retrospective studies, and 1 case report. Only 1 RCT (n=156, age range 6-60 months), 1 prospective observational study (n=23, age range 17-84 months), 1 retrospective study (n=67, age range 1-180 months) and 1 case series (n=2) included mannitol as a treatment arm (total n= 248). The dose of Mannitol administered ranged from 0.25-1.0 g/kg across the studies. The majority of the studies did not report any side effects. The retrospective study reported renal failure in one patient.

The RCT compared mannitol with placebo for the management of raised intracranial hypertension due to cerebral malaria. No serious side effects were reported (such as hypersensitivity reaction, vomiting, and significant change in renal function or pulse or blood pressure, exacerbation of heart failure or pulmonary edema). There was no significant difference in the mortality between the placebo (13/80 or 16.3%) and mannitol (10/76 or 13.2%) groups: RR=1.2 (95% CI 0.5 to 2.7) and the authors concluded that mannitol had no significant impact on clinical outcome of cerebral malaria.

The prospective observational study did not compare mannitol to any other medicines or placebo. It demonstrated and concluded that mannitol reduced ICP, but it did not prevent or control severe intracranial hypertension.

The retrospective study compared mannitol with co-administration of mannitol and hypertonic saline (HS) or HS alone for the treatment of cerebral oedema due to infection, haemorrhage, anoxia and metabolic factors. Duration of comatose state and mortality rate were significantly lower in the combined mannitol/HS group and HS alone group than the mannitol group (duration of comatose state 87.5 ± 26.1 vs. 88.6 ± 42.5 vs. 123.0 ± 48.2 respectively, p=0.004); Mortality 20% vs. 25% vs. 50% respectively, p = 0.003).

The case series described the use of mannitol in the management of ICP secondary to traumatic brain injury with the addition of HS if the ICP was not adequately maintained. The use of Mannitol reduced ICP temporarily, but had an adverse effect on CPP (substantial decrease). The subsequent use of HS reduced ICP and maintained or improved CPP.
This systematic review concluded that compared to osmotic agents, HS appeared to cause a greater reduction in ICP. The outcome of bacterial meningitis in children is improved after administration of oral glycerol. It appears that a sustained reduction of ICP can be achieved by modifying the modes and rates of administration of these osmotic agents but further studies and investigations are needed to identify the most effective medicine.

Individual studies (categorized by therapeutic use of mannitol):

Mannitol use in Cerebral Oedema (See Appendix 3, Table 4)

Six studies (comparative=2, retrospective=3, case report=1) with a total n=231 investigated the use of mannitol in cerebral oedema in children (overall age range of 0-17 years). The dose of mannitol used ranged from 0.18-2.5 g/kg. A paired comparison study (Miller, 1993) reported that mannitol was more effective in children with focal traumatic brain injury (TBI). Generally no serious side effects were reported. A case series study (Smaik, 1989) reported that surviving craniocerebral gunshot wound victims benefited from mannitol as a measure to control ICP. However, a comparative study (MacDonald, 1982) concludes that 20% glycerol is as effective as 20% mannitol. Moreover, one retrospective study (Vats, 1999) emphasizes that there is a lower relative risk of death with the use of hypertonic saline compared to mannitol. Due to the lack of RCTs for the use of mannitol in paediatric population with cerebral oedema, the nature of the studies, small sample size, and mixed reports regarding the therapeutic benefits of mannitol in cerebral oedema, it is not possible to make a definite recommendation for the role of mannitol in the therapeutic management of cerebral oedema caused by TBI.

Mannitol use in DKA (See Appendix 3, Table 5)

One prospective study (age range: 7 months- 20 years) and 1 case series (age range: 2.5-17 years) (total number of participants = 46), investigated the use of mannitol in DKA in children. The same dose of mannitol (0.25-1 g/kg IV) was used in both studies. The prospective study did not compare mannitol with any other medications or placebo and concluded that 17/35 patients who responded to mannitol had significantly improved clinical outcomes. The case series did not compare mannitol to any other medications or placebo and reported that survival was 100% in 10 cases treated early with mannitol. Neither study stated any side effects. Overall, the prospective study used a multifaceted intervention, including mannitol, to manage cerebral oedema caused by DKA. This study recommends the timely administration of mannitol as an integral part of therapy for raised ICP. The case series did not compare mannitol with any other medications or placebo and concluded that mannitol should be given to children with cerebral oedema. Due to lack of RCTs and the observational nature of the included studies and their small sample size, it is not possible to make a definite recommendation for inclusion of mannitol in the therapeutic management of cerebral oedema caused by DKA.

Mannitol use in asthma (See Appendix 3, Table 6)

Four studies: 1 multi-centre randomized controlled trial (age range: 6-50 years) and 3 observational prospective cohort studies (with overall age range of 6-21 years), total n=589, investigated the use of mannitol challenge test in asthma in paediatrics. The same dose of dry powder mannitol (0.5-10.20, 40, 80, 160,160,160 mg) was used in all of these studies. The multi centre randomized controlled trial did not state any particular benefits for the use of mannitol compared to Methacoline test. One of the observational prospective cohort studies stated that mannitol was generally well tolerated. The second one stated that mannitol challenge test was faster to perform than the

† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.
Methacoline test. The third study stated that mannitol challenge was well tolerated by all subjects. The multi-centre randomized controlled trial and one of the observational prospective cohort studies did not state any side effects. One of the observational prospective cohort studies reported cough in one of case that prevented completion of the mannitol challenge test. Another observational prospective cohort study reported that during the mannitol challenge, 3 children developed persistent cough and the challenge test was terminated. Overall, one of the observational prospective cohort studies did not compare mannitol to any other agent or placebo and concluded that assessment of airflow obstruction with mannitol challenge is a reliable alternative in patients that cannot perform repeated spirometry. The multi-centre randomized controlled trial compared mannitol to Methacoline and concluded that sensitivity and specificity were equivalent for mannitol and Methacoline clinical diagnosis of asthma. Two observational prospective cohort studies compare mannitol with Methacoline and one concluded that mannitol challenge test is a suitable alternative to assess EIB in asthmatic children. The other one conclude that mannitol challenge test is reliable and is done faster than Methacoline challenge test.

The multi centre randomized controlled trial had a large enough sample size and it concluded that sensitivity and efficacy of mannitol and Methacoline challenge tests are the same. The nature of the 3 observational prospective cohort studies and their small sample sizes does not offer a robust justification for considering mannitol challenge test as an alternative to the Methacoline challenge test.

**Mannitol use in Cystic Fibrosis (See Appendix 3, Table 7)**

Four studies (2 randomized double blind placebo controlled cross over studies, 1 randomized trial [open cross over study], and 1 observational study) investigated the use of inhaled mannitol as a therapeutic measure in children with cystic fibrosis (total n=132 with the overall age range of 8-18). The dose of mannitol used across the studies was of 420-475 mg. One of the randomized double blind placebo controlled cross over studies reported that regular treatment with inhaled mannitol increases the hydration and changes the surface properties favourably in patients with CF. These changes lasted for 12 hours after the last mannitol treatment and correlated significantly with the improvement in lung function in response to inhaled mannitol. Another one of the randomized double blind placebo controlled cross over studies reported a 7% mean relative increase in the FEV1 from baseline after treatment with mannitol. The randomized trial reported that 3 months treatment with inhaled mannitol was as effective as rhDNAse and resulted in 7% increase in FEV1. The observational study reported that 24% of children with CF had a positive airway challenge with mannitol. One of the randomized double blind placebo controlled cross over studies and the randomized trial did not state any side effects.

One of the randomized double blind placebo controlled cross over studies reported 7 serious adverse events which were not considered treatment related and none resulted in death. The observational study reported cough as a common SE, as well as vomiting (n=2), dizziness and chest tightness (n=1), and nausea (n=1). Overall, both randomized double blind placebo controlled cross over studies compare mannitol with placebo and one concluded that placebo had no significant effect on sputum properties and the other study concluded that a 2-week administration of inhaled dry-powder mannitol BID improves FEV1 and FEF. The randomized trial compared mannitol with rhDNAse alone and in combination with mannitol and concluded that mannitol was as effective as rhDNAse in treatment of CF in children but the co-administration of the two agents was not beneficial. In spite of the small sample size for the randomized double blind placebo controlled cross over studies and the nature of the other two studies and their small sample size, it seems rational to use inhaled dry powder mannitol as an alternative to rhDNAse in treatment of CF in children.

† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.
Mannitol use in other indications (See Appendix 3, Table 8)

Seven studies (1 randomized control trial, 1 control trial, 1 prospective study, 1 descriptive retrospective study, 3 case series) with a total \( n = 214 \) and overall age range of neonates to 16 years old investigated the therapeutic use of mannitol in different clinical situations, such as managing renal ischemic damage, treatment of diuretic resistant oedema in nephritic syndrome, differentiation of renal failure from pre-renal failure, prophylactic mannitol during sequential dialysis, and evaluating the role of mannitol in causing hyponatremia or interrupting phosphorous concentration. The dose of Mannitol used varied from study to study with an overall range of 0.25-1.0 g/kg. Four of these studies did not state any therapeutic benefits for mannitol. None of the studies stated any side effects.

The randomized control trial (Ridgen, 1984) reported significant decrease of plasma creatinine level and urinary albumine excretion upon administration of mannitol, when compared with Hartmann's solution, which indicates that mannitol can protect the kidney from ischemic damage due to hypoperfusion and children who received mannitol had a more rapid recovery of plasma creatinine and less albuminuria.

The control trial (Soriano, 1996) reported increased osmolality, decreased hematocrite and increased resistance in the distal and middle cerebral arteries upon administration of mannitol. This trial compared cerebral blood flow before and after mannitol infusion and concluded that mannitol briefly reduces the cerebrovascular resistance and reduces the cerebral blood volume.

One case series (Daljit, 2009) reported that mannitol significantly increased the mean treatment ultrafiltration volume and it halved the odds of intradialytic symptoms and hypotension/premature discontinuation of dialysis. This study compared mannitol and no mannitol in children undergoing hemodialysis and concluded that prophylactic use of mannitol reduces the intracranial symptoms and hypotension and it can treat milder degrees of disequilibrium, thus allowing treatment to go to completion.

The prospective study (Oommen, 1980) compared mannitol with saline to measure urine output to differentiate renal failure from pre-renal oliguria and concluded that mannitol had no clear diagnostic benefit. The descriptive retrospective study (Rando, 2009) compared the plasma sodium level in children who underwent craniofacial surgery and received or did not receive mannitol. Hyponatremia occurred frequently in these children and it was unrelated to the administration of mannitol.

A case series (Ruf, 2003) study compare mannitol with craniectomy and concluded that decompressive craniectomy should be considered in case of sustained increase in ICP (20 mmHg). Another case series (Lewis, 1999) showed the beneficial effects of mannitol and frusemide combination therapy in the treatment of diuretic resistant oedema in 3 children with nephritic syndrome.

The RCT and controlled trial had small sample sizes and although both reported therapeutic benefits for mannitol, it is difficult to draw a rational and definite conclusion from them. There is not enough evidence to recommend mannitol as an alternative to Hartmann's solution in the management of ischemic renal damage. Due to the small sample size and the observational design of the other studies, none of the other study conclusions are robust enough to draw a definite conclusion for recommending mannitol as a diagnostic measure in differentiating renal and pre-renal cause of oliguria, or adjunct measure in children undergoing hemodialysis, or in severe increased ICP.

† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.
List of clinical trials, listed on ClinicalTrial.gov, including the use of mannitol or hypertonic saline in children with elevated ICP

Only one clinical trial entitled "Mannitol as Adjunct Therapy for Childhood Cerebral Malaria" (NCT 00113854) was found targeting the children between the ages of 6 months - 5 years old. This trial seeks to establish whether a single dose of intravenous mannitol given to children with cerebral malaria will significantly reduce the coma recovery time. This clinical trial is sponsored by the Makerere University, Uganda. The estimated study completion date was May 2005; however, we did not find any published result for this trial.

Two studies including the use of hypertonic saline (HS) in children with traumatic brain injury (TBI) were found. One of them, "Feasibility trial of Traumatic brain Injured Patients Randomized in the Prehospital Setting to Either Hypertonic Saline and Dextran Versus Normal Saline" was sponsored by St. Michael's Hospital in Toronto, has been completed (NCT00878631). However, this study included patients 16 years old or older. Another clinical trial, "Use of Salt-Water Solution to Improve Symptoms in Concussion"(NCT00142090) was sponsored by Rady Children's Hospital in San Diego and has been completed. The purpose of this study is to find out if 3% hypertonic saline (salt-water solution) given in a vein improves the headache that may be caused by a concussion. 3% hypertonic saline may also improve some of the other symptoms that may be caused by concussion (for example: confusion, nausea, vomiting). This trial included patients between 6-17 years old who are admitted for observation of closed head injury; however, we did not find any published result for this trial.

Discussion

Traumatic brain injury places a substantial burden on health care system worldwide. Management of elevated ICP is one of the main components of the management of TBI. Administration of mannitol has become the corner stone in the treatment of patients with severe head injury and elevated ICP particularly in the acute management phase in both adults and children. In 2008, Sherry et al stated that despite the lack of large prospective trials using mannitol in the treatment of cerebral oedema, early administration has been associated with an improvement in cerebral oedema in case reports[23].

This review did not find any well-controlled clinical trials demonstrating a significant impact of mannitol administration for the treatment of elevated ICP in children. Multiple observational studies provide data on the mechanism by which mannitol works; however, there have been no controlled clinical trials against placebo or other hyperosmolar agents in paediatric patients nor are there data to validate different regimens of mannitol administration. Reported, mannitol side effects include development of acute renal failure and rebound cerebral oedema. Data from adult studies indicate a risk for development of acute tubular necrosis and renal failure because mannitol is excreted unchanged in urine [27]. It is important to note that there is a paucity of pharmacokinetic and pharmacodynamics data for mannitol use in children. In addition, we did not find any study that has reported long-term safety and efficacy data for the use of mannitol in children. It seems that there is a lack of firm evidence of a favourable effect of mannitol in children and the majority of the information has, inevitably, been extrapolated from adult studies. We did not find any study emphasizing dose, efficacy, and side effects of mannitol in children.

In 2008, a Cochrane systematic review concluded that "there is insufficient reliable evidence to make recommendations on the use of mannitol in the management of patients with traumatic brain injury. There are many unanswered questions regarding the optimal use of mannitol following acute traumatic head injury. The widespread current use of mannitol, and lack of clarity regarding optimal administration, presents an ideal opportunity for the conduct of randomized controlled trials". [28].

† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.
In 2009, a Cochrane systematic review concluded that there were no randomized or quasi-randomized controlled trials on the efficacy and safety of mannitol or urea to support their use as adjuncts for treating cerebral malarial [29]. However, neither of these reviews reported specific data for children. These limitations underscore the urgent need for more research to establish adequate risk-benefit profiles and appropriate dosing regimen for mannitol used in children.

Other alternatives to reduce the elevated ICP are HS and oral glycerol. A review article by Qureshi et al, 2000, states that “all human studies published to date reporting on the use of HS in treatment of cerebral edema and elevated ICP only include case reports, case series, and small controlled groups. A uniform concentration of HS has not been studied, dose-response curves are lacking, and the safety and efficacy of these solutions need to be further evaluated; however, the low frequency of side effects and definite reduction of ICP observed with use of HS in these studies are very promising”[30]. The systematic review by Gwer et al concluded that HS appears to achieve a greater reduction in ICP than other osmotic agents. Oral glycerol seems to improve outcome among children with acute bacterial meningitis. We did not find any ongoing or upcoming clinical trials including glycerol and our target population or clinical trials including HS and our target population for the management of cerebral oedema.

**Conclusion and recommendations for the Expert Committee on the use of mannitol in children**

The use of mannitol in pediatric population depends on experience and reason rather than on evidence-based studies in children. Mannitol has been widely used in infants and children, but its beneficial effects in children are still not clearly established. The WHO model formulary for children and BNF recommend mannitol for the management of raised ICP in children.

Elevated ICP is a serious condition that needs immediate and aggressive medical interventions. Elevated ICP can be the result of TBI, DKA, encephalopathies, and last but not least child abuse. Reducing the elevated ICP is necessary to prevent the mortality and morbidity associated with cerebral oedema. Mannitol has been the cornerstone of elevated ICP management for decades; however, its therapeutics effects are still debated and the pharmacodevelopmental aspects of its use in infants and children are also incompletely studied. The clinical decision to use mannitol needs special diagnostic and clinical skills and training as well as specific treatment facilities and medical devices such as syringe with in-line filter. Continual assessment of neurologic status, including ICP monitoring, is required to assess the need for administration of mannitol. No English language studies focusing on the pharmacodynamics and pharmacokinetics of mannitol in children or its long term efficacy and side effects in children was found through our search of several different international databases.

The majority of studies in children are observational in nature and had small sample sizes. Moreover, the results of these small studies are contradictory in most cases. For example, a systematic review by McGuire et al reports that a single dose of mannitol was no more effective at reducing mortality rates in neonates with asphyxia compared with no drug treatment. Another systematic review by Whitelaw et al concludes that no definite recommendation regarding the use of mannitol in hypoxic-ischemic brain injury in the perinatal period can be made. A systematic review by Gwer concluded that compared to osmotic agents, HS appeared to cause a greater reduction in ICP in children. It is important to note that the other therapeutic alternatives to reduce cerebral oedema, such as HS and oral glycerol have not been the subject of a RCT in children either. Due to the lack of robust clinical evidence for the therapeutic use of mannitol or HS or oral glycerol in children, it is hard to make a definite recommendation for inclusion of any of these agents in the management strategy of elevated ICP in children. A multicenter RCT is needed to evaluate the

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therapeutic effects of mannitol in children 0-12 years old and provide the much needed basis for selection of mannitol or potential new agents for a particular and more effective therapeutic purpose.

Mannitol has also been used in other clinical situations such as mannitol challenge test in asthma and as a therapeutic measure in cystic fibrosis. Dry powder mannitol had shown some promise in the treatment of cystic fibrosis in children. However, there is no RCT supporting these findings and despite the importance of clinical management of cystic fibrosis due to the nature of this disease, it is not considered a health priority in developing countries. Overall, the published studies are of various natures and usually are either retrospective, observational, or case series with small sample sizes. There is no specific RCT study comparing mannitol to HS in children, nor there is safety and efficacy data for our target population.
† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.

References:

7. Drugs @FDA
13. CDC.gov
27. Knapp, James M. Hyperosmolar Therapy in the Treatment of Severe Head Injury in Children mannitol and Hypertonic Saline. AACN Clinical issues. Volume 16, Number 2, pp.199-211)

† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.
Appendix 1: Search terms

Pubmed

2. "Mannitol"[Mesh] OR Osmitrol OR Osmofundin

Embase
1. 'review'/exp OR 'review' OR 'medline'/exp OR medline OR 'medlars'/exp OR medlars OR 'pubmed'/exp OR pubmed OR 'scisearch'/exp OR scisearch OR 'psychlit'/exp OR psychlit OR 'psychinfo'/exp OR psychinfo OR 'electronic databases' OR 'electronic database' OR hand NEAR/5 search* OR manual* NEAR/5 search* OR bibliographic NEAR/5 database* OR pooled NEAR/5 analy* OR pooling OR veto OR sesimonian OR fixed NEAR/5 effect OR 'mantel haenszel' OR 'meta analysis'/exp OR 'meta analysis' OR 'retracted article'/exp OR 'retracted article' OR systematic* NEAR/5 review* OR systematic* NEAR/5 overview* OR quantitative* NEAR/5 review* OR quantitative* NEAR/5 overview* OR integrative NEAR/5 review* OR research NEAR/5 integration OR quantitative* NEAR/5 synthesis* OR embase:ti

2. "Mannitol"[Mesh] OR Osmitrol OR Osmofundin

3. 'child'/exp OR 'child' OR 'children'/exp OR 'children' OR 'youth'/exp OR 'youth' OR youth* OR newborn* OR 'newborn'/exp OR 'newborn' OR 'new born' OR 'childhood disease'/exp OR 'childhood disease' OR 'baby'/exp OR 'baby' OR 'infant'/exp OR 'infant' OR infant* OR childhood* OR toddler* OR kid OR kids OR 'young patient' OR boy* OR girl* OR 'young age' OR paediatr* OR paediatr* OR 'child death'/exp OR 'child death' OR 'child health'/exp OR 'child health' OR 'child care'/exp OR 'child care' OR 'childhood mortality'/exp OR 'childhood mortality' OR 'child hospitalization'/exp OR 'child hospitalization' OR 'pediatric hospital'/exp OR 'pediatric hospital' OR child*
Appendix 2: Search strategy and article selection

**Pubmed**


Results: 1866521 citations

2. Search "Mannitol"[Mesh] OR "Osmotrol" OR "Osmofundin"

Results: 17389 citations

3. Search (# 1) AND # 2

Results: 814 citations

4. Search (mannitol) AND systematic[sb]

Results: 82 citations

- 82 systematic reviews retrieved for mannitol, after reviewing the titles of these sys reviews, we considered 51 as relevant to our sys review. After reviewing the abstracts, 40 citations were considered relevant for further review. Upon reviewing the full text, only 8 citations were considered relevant to our review and 32 citations were excluded (Non-English= 4, Not our target population=13, Mannitol not included=9, not clear if pediatric pop was included or not or we were not able to extract the pediatric data=5, Survey=1). After the last review, we only considered 4 sys review and the other 4 were excluded (1 not included our target population, 1 was an expert opinion, 1 was a teaching article, 1 was an overview not a systematic review)

**Embase**

1. 'review'/exp OR 'medline'/exp OR 'medlars'/exp OR 'pubmed'/exp OR 'scisearch'/exp OR 'psychlit'/exp OR 'psyclit'/exp OR 'psychinfo'/exp OR 'electronic databases' OR 'electronic database' OR hand NEAR/5 search* OR manual* NEAR/5 search* OR bibliographic NEAR/5 database* OR pooled NEAR/5 analys* OR pooling OR pot OR sesimonian OR fixed NEAR/5 effect OR 'mantel haenszel' OR 'meta analysis'/exp OR 'retracted article'/exp OR systematic* NEAR/5 review* OR systematic* NEAR/5 overview* OR quantitative* NEAR/5 review* OR quantitative* NEAR/5 overview* OR methodologic* NEAR/5 review* OR methodologic* NEAR/5 overview* OR integrative NEAR/5 review* OR research NEAR/5 integration OR quantitative* NEAR/5 synthesi* OR embase:ti

Results: …citations

2. 'child'/exp OR 'child' OR 'children'/exp OR 'children' OR 'youth'/exp OR 'youth' OR youth* OR newborn* OR 'newborn'/exp OR 'newborn' OR 'newborn' OR 'new born' OR 'childhood disease'/exp OR 'childhood disease' OR 'baby'/exp OR 'baby' OR babies OR 'infant'/exp OR 'infant' OR infant* OR childhood* OR toddler* OR kid OR kids OR 'young patient' OR boy* OR girl* OR 'young

† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.
Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.

20

Results: 3,167,860 citations

3. 'mannitol'/exp OR mannitol OR 'osmitrol'/exp OR osmitrol OR 'osmofundin'/exp OR osmofundin
   Results: 27,063 citations

4. (#1) AND (#2) AND#3
   Results: 484 citations

Cochrane Library

34 systematic reviews were identified; however none met our inclusion criteria

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**Appendix 3: Data extraction tables**

**Table 1: William McGuire. 2007. Systematic review: Perinatal Asphyxia.**

Question: What are the effects of interventions in term or near-term newborns with perinatal asphyxia?

# of studies included: 7 systematic reviews, 2 case series, 7 RCTs, only one small RCT (n=25) included mannitol

<table>
<thead>
<tr>
<th>Citation &amp; Date</th>
<th>Study Design</th>
<th>Age range</th>
<th># of patients</th>
<th>Intervention &amp; Dose</th>
<th>Comparison</th>
<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adhikari M. 1990</td>
<td>Small RCT</td>
<td>Term neonates</td>
<td>25</td>
<td>Mannitol, single dose 1 g/kg</td>
<td>No drug treatment</td>
<td>Mortality and neurological impairment</td>
<td>Not stated</td>
<td>Not stated</td>
<td>A single dose of Mannitol is no more effective at reducing mortality rates in neonates with asphyxia compared with no drug treatment. Similar mortality in both groups (AR 4/12 [33%] with mannitol v 4/13 [31%] with no drug treatment; RR 1.08, 95% CI 0.35 to 3.40. No data were available on long-term neurodevelopmental outcomes.</td>
</tr>
</tbody>
</table>

† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.

Objective: To identify and to evaluate controlled trials of interventions for term infants developing hypoxic-ischemic encephalopathy

# of studies included: 1 uncontrolled study, 4 clinical trials, 3 randomized trials, 1 randomized double blind trial, 1 randomized trail, 1 retrospective case study, 2 Case series, and 2 randomized trials. Only 1 case reports, 1 observational study, and one uncontrolled study included mannitol.

<table>
<thead>
<tr>
<th>Citation &amp; Date</th>
<th>Study Design</th>
<th>Age range</th>
<th># of patients</th>
<th>Intervention &amp; Dose</th>
<th>Comparison</th>
<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marchal C 1974</td>
<td>Uncontrolled study</td>
<td>Full Term infants</td>
<td>225</td>
<td>Mannitol, repeated doses , 1 g/kg IV</td>
<td>Receiving Mannitol before(n=130) or after 2 hours(n=95)</td>
<td>Not stated</td>
<td>Improved prognosis. 130 infants received 1 g/kg IV mannitol before 2 h and 95 received mannitol after 2 h. There was a lower proportion of deaths and of disabled infants at 1 year in the group who received mannitol before 2 h but, as the groups were not randomized, no conclusion about the efficacy of early mannitol is justified</td>
<td>Not stated</td>
<td>Groups were not randomized and no conclusion about efficacy of early mannitol is justified</td>
</tr>
<tr>
<td>Citation &amp; Date</td>
<td>Study Design</td>
<td>Age range</td>
<td># of patients</td>
<td>Intervention &amp; Dose</td>
<td>Comparison</td>
<td>Outcomes considered</td>
<td>Benefits</td>
<td>Side effects</td>
<td>Results/Comments</td>
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</tr>
<tr>
<td>Levene MI 1985</td>
<td>Observational study</td>
<td>Infants</td>
<td>10</td>
<td>20% Mannitol, 1 g/kg IV over 20 minutes</td>
<td>Dexamethasone (4 grams IV) in 7/10 infants</td>
<td>Reducing ICP</td>
<td>Fall in ICP and rise in cerebral perfusion 60 minutes after starting the infusion</td>
<td>Not stated</td>
<td>7/10 infants had the criteria for treatment of elevated ICP and they received Dexamethasone. 3/7 infants had raised ICP six hours after Dexamethasone treatment and they received mannitol infusions 7, 7.5, and 18 hours later. In 5/7 infants ICP decreased within 1 h after dexamethasone and in a sixth one within 2 h. In 1/7 infant, there was no reduction of ICP within 24 h after treatment. 4/10 infants who received mannitol were studied 60 minutes before and 300 minutes after the mannitol infusion. Within 20 minutes of the mannitol infusion, all infants had significant drop in ICP.</td>
</tr>
</tbody>
</table>

† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.
<table>
<thead>
<tr>
<th>Citation &amp; Date</th>
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<th>Comparison</th>
<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levene MI 1987</td>
<td>Case reports</td>
<td>Infants</td>
<td>23</td>
<td>20% Mannitol, 1 g/kg IV</td>
<td>info not available from abstract</td>
<td>info not available from abstract</td>
<td>info not available from abstract</td>
<td>info not available from abstract</td>
<td>Mannitol infusion seems of value in treating raised ICP associated with cerebral oedema and its cautious use is recommended if ICP monitoring is available 9 infants with sustained ICP&lt;15mmHg dies or survived with disability in spite of mannitol</td>
</tr>
</tbody>
</table>

† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.

Objective: To determine the current evidence of the effectiveness of osmotic agents and their effect on resolution of coma and outcome in children with acute encephalopathy.

# of studies. 4 RCTs, 3 prospective observational studies, 2 retrospective studies, and 1 case report. Only 1 RCT (n=156), 1 prospective observational study (n=23), 1 retrospective study (n=67) and 1 case reports (n=2) included mannitol.

<table>
<thead>
<tr>
<th>Citation &amp; Date</th>
<th>Study Design</th>
<th>Age range</th>
<th># of patients</th>
<th>Intervention &amp; Dose</th>
<th>Comparison</th>
<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Namutangula 2007 Emergency Paediatric Ward of Mulago Hospital, Uganda's national referral and teaching hospital</td>
<td>Randomized double-blind placebo controlled clinical trial</td>
<td>6-60 months</td>
<td>156</td>
<td>Mannitol, single IV bolus dose 1 g/kg (5 mL/kg of 20% mannitol)</td>
<td>Placebo (Normal saline 5 mL/kg IV)</td>
<td>Clinical outcome (time to regain consciousness, time to sit unsupported, time to start oral feeds, and duration of hospital stay)</td>
<td>None stated</td>
<td>No adverse effect were observed after administration of mannitol (no hypersensitivity reaction or vomiting or significant change in renal function or pulse or blood pressure or exacerbation of heart failure or pulmonary oedema was not observed).</td>
<td>Time to gain consciousness (p=0.11), sit unsupported (p=0.81), time to start oral intake (p=0.13) and total coma duration (p=0.07) were similar in both groups. There was no significant difference in the mortality between the placebo (13/80 or 16.3%) and mannitol (10/76 or 13.2%) groups: RR=1.2 (95% CI 0.5 to 2.7) Mannitol had no significant impact on clinical outcome of cerebral malaria. It is difficult to recommend intravenous mannitol as adjunct therapy for childhood malaria</td>
</tr>
<tr>
<td>Newton CR 1997 Prospective observational study</td>
<td>17-84 months</td>
<td>23</td>
<td>Mannitol 0.5-1.0 g/kg infused over 10-20 minutes</td>
<td>None</td>
<td>Neurological outcome</td>
<td>None stated</td>
<td>None stated</td>
<td>Although mannitol reduced ICP and appeared to control the ICP in children with intermediate intracranial hypertension, it neither prevented nor controlled severe intracranial hypertension</td>
<td></td>
</tr>
<tr>
<td>Yildizdas D 2006 Pediatric Intensive Care Unit,</td>
<td>Retrospective study</td>
<td>1-180 months</td>
<td>67</td>
<td>Mannitol 0.5 g/kg for the first two doses and if needed the HS or both HS and Mannitol</td>
<td>Duration of comatose state, mortality</td>
<td>Renal failure in one patient who received mannitol and mannitol had</td>
<td>Although there was no statistically significant difference in the highest serum Na and osmolarity levels of the groups,</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.
<table>
<thead>
<tr>
<th>Citation &amp; Date</th>
<th>Study Design</th>
<th>Age range</th>
<th># of patients</th>
<th>Intervention &amp; Dose</th>
<th>Comparison</th>
<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pcukurova University, School of medicine, Adana, turkey</td>
<td></td>
<td></td>
<td></td>
<td>groups GI (n=22) only received mannitol, GII (n=25) only received HS and GIII (n=20) received either HS and mannitol together or HS after mannitol had been stopped.</td>
<td>maintenance dose of 0.25 g/kg/dose</td>
<td></td>
<td>been stopped. 2 patients who received HS and one patient who received both mannitol and HS developed diabetes insipidus and HS treatment was terminated. 2 patients who received HS and 2 patients who received both HS and mannitol developed hyperchloremic metabolic acidosis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berger S 2002</td>
<td>Case reports</td>
<td>11-12 years</td>
<td>2</td>
<td>Mannitol , 100 mL of 20% solution(2.2 mL/kg) via a central venous line over 30 minutes</td>
<td>Saline is not the comparator. Both cases received saline later because mannitol was not effective 20% NaCl solution(0.67 mL/kg)</td>
<td>Not stated</td>
<td>Non stated</td>
<td>Non stated</td>
<td>When compared to mannitol, HS maintained or improved CPP (cerebral perfusion pressure), an important determinant of neurological outcome.</td>
</tr>
</tbody>
</table>

† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.
Table 4: Mannitol use in cerebral edema.

<table>
<thead>
<tr>
<th>Citation &amp; Date</th>
<th>Study Design</th>
<th>Age range</th>
<th># of patients</th>
<th>Intervention &amp; Dose</th>
<th>Comparison</th>
<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacDonald 1982</td>
<td>Comparative study</td>
<td>2-15</td>
<td>14</td>
<td>20% Mannitol, 0.5-1 g/kg</td>
<td>Glycerol 20%</td>
<td>ICP</td>
<td>Glycerol and Mannitol were both equally effective in lowering ICP</td>
<td>Not stated</td>
<td>Authors recommend infusions of 20% glycerol or 20% mannitol at a dose of 0.5-1.0 gm per kilogram</td>
</tr>
<tr>
<td>White 2001</td>
<td>Retrospective study</td>
<td>0-17 years</td>
<td>136</td>
<td>Mannitol dose not mentioned</td>
<td>None stated</td>
<td>Paediatric Trauma Score, Glasgow Coma Scale, Paediatric Risk of Mortality,</td>
<td>None stated</td>
<td>Mannitol administration was associated with prolonged length of stay and increased cost without improving survival rate or neurologic function. Authors suggest re-evaluation of blood pressure targets and mannitol use in children with severe traumatic brain injury.</td>
<td></td>
</tr>
<tr>
<td>Vats 1999 Egleston Children's Hospital at Emory University, Atlanta, USA</td>
<td>Retrospective study</td>
<td>9 months - 16 years</td>
<td>25+18=43 (12/43 received both mannitol and HS)</td>
<td>Mannitol 20%, 0.5-1 g/kg (n=18)</td>
<td>HS, 5mL/kg (n=25)</td>
<td>ICP</td>
<td>Both HS and mannitol produced significant and sustained reduction in ICP, however, HS resulted in significant and sustained increase of cerebral perfusion pressure</td>
<td>None stated</td>
<td>Significant reduction in ICP at 30 min and at 60 and 120 min following the HS administration. Significant ICP reduction at 60 and 120 minutes after receiving mannitol (the ICP of the patients receiving mannitol was significantly higher than those receiving HS prior to the treatment and at 60 and 120 min. 12 patients who received both HS and mannitol had significant and sustained decrease in ICP. Definitive conclusion regarding the use of HS in the treatment of increased</td>
</tr>
</tbody>
</table>

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<th>Benefits</th>
<th>Side effects</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>James 1980</td>
<td>retrospective study</td>
<td>Mean age 14 years</td>
<td>18</td>
<td>Mannitol(0.18-2.5 g/kg per dose)</td>
<td>None stated</td>
<td>ICP</td>
<td>In 97% of the time, bolus dose of mannitol reduced ICP</td>
<td>None stated</td>
<td>Other concomitant therapies included dexamethasone, neuromuscular blockade, perventilation, barbiturates and hypothermia, in refractory cases</td>
</tr>
<tr>
<td>Sarnaik 1989</td>
<td>case reports</td>
<td>1-12 years</td>
<td>14 (5/14 were morbid upon arrival, 3/14 were alert and stayed alert, 6/14 were comatose upon arrival and 5/6 eventually regained consciousness)</td>
<td>Mannitol, IV bolus 0.5-1 g/kg to all comatose patients(n=6) to manage ICP in addition to surgical intervention</td>
<td>None stated</td>
<td>Glasgow Coma Scale</td>
<td>None stated</td>
<td>None stated</td>
<td>Although serious cognitive deficits were noted, all craniocerebral gunshot wounds(GSW) survivors had sufficient functional recovery to warrant aggressive cardiopulmonary resuscitation and measures to control ICP in the management of comatose victims of craniocerebral GSW</td>
</tr>
<tr>
<td>Miller 1993</td>
<td>paired comparison</td>
<td>3-17 years old</td>
<td>6</td>
<td>Mannitol(0.5 g/kg)</td>
<td>Hypotonic drugs (thiopentone &amp; gamma-hydroxybutyrate)</td>
<td>Refractory ICP</td>
<td>Mannitol more effective in focal TBI</td>
<td>None stated</td>
<td>Hypotonics were superior in younger patients with diffuse rather than focal brain injury were</td>
</tr>
</tbody>
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### Table 5: Mannitol use in DKA

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</tr>
</thead>
<tbody>
<tr>
<td>Fiordalisi 2007 Kings County Hospital Center, NY, Children’s Hospital of Buffalo, NY, and Children’s Hospital, University Health Systems of Eastern North Carolina, NC, USA</td>
<td>Prospective study - multifaceted intervention (circulatory resuscitation, assigning volume of deficit and rate of total fluid administration, electrolyte content of IV solutions after the first hour, electrolyte supplementation, insulin, cardiorespiratory monitoring, and mannitol administration)</td>
<td>7 months-20 years</td>
<td>35/635 patients received mannitol</td>
<td>Mannitol 0.25-1 g/kg IV to 35/635 patients</td>
<td>None stated</td>
<td>Clinical improvement within 30 min of mannitol infusion; complete neurological recovery</td>
<td>The mannitol-responsive group (n=17/35) had statistically significant improvement in outcome</td>
<td>None stated</td>
<td>The authors point out that due to the observational nature of their study, it is not possible to attribute outcomes to any one feature of the therapy. They also add that clinical vigilance by experienced clinicians and timely administration of mannitol when raised ICP is suspected is integral part of their therapeutic approach.</td>
</tr>
<tr>
<td>Roberts 2001 Denver Children's Hospital, Denver, USA</td>
<td>Case reports</td>
<td>2.5 - 17 years</td>
<td>11</td>
<td>Mannitol, 0.25-1 g/kg IV to 10/11 surviving children</td>
<td>None stated</td>
<td>Neurologic status</td>
<td>Survival was 100% in 10 children who were treated early with mannitol (9/10 had mannitol when early CNS symptoms appeared and all 10 patients received mannitol before</td>
<td>The only death occurred in the 17 y/o patient who had intracerebral complications and no mannitol treatment about 24 h before</td>
<td>The authors emphasize that all children with severe DKA (PH&lt;7.10) should be admitted to PICU and be attended by healthcare professionals who are knowledgeable in managing. Mannitol must be</td>
</tr>
</tbody>
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<td>cardiopulmonary arrest.</td>
<td>referral to the hospital</td>
<td>kept in the warming oven and be immediately administered if diagnostic signs of cerebral edema appears and it should be given 0.5-1 g/kg over 30-60 min and repeated as needed. DKA and cerebral edema Mannitol should be given promptly for the treatment of intracerebral complications indicated by the clinical course even if cerebral edema is not documented by a computed tomography.</td>
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</table>
| Kersten 2009  
Outpatient clinic of the pediatric department of the Medisch Spectrum Twente, Enschede, The Netherlands (pulmonary function laboratory) | observational prospective cohort | 9-18 years | 25/33(n=8 were excluded: 2 did not perform both tests, 3 experienced persistent cough and the test was terminated, 3 had changes in medications between the challenges) | Mannitol(0.5,10.20,40,80,160,160,160 mg) at the second visit | Exercise challenge test in cold air at the first visit | Exercise-induced bronchoconstriction (EIB) | Mannitol was generally well tolerated and no serious adverse event reported | During the challenge, all children developed a mild cough and in 3 children cough was persistent enough to terminate the challenge. Coughing can a limitation of the mannitol challenge test if it prolongs the between inhalation and spirometry it can lead to a milder osmotic stimulus and give false negative results | Baseline FEV1 in n=25 before mannitol had a normal distributions with a mean±SD of 97.4±16.6%predicted value which was not different from baseline before exercise (99.3±20.1 predicted value). Geometric mean [95% CI] for the response-dose ratio (RDR) for mannitol was 0.0086[CI: 0.0031-0.02475] and geometric mean [95%CI] for the PD15 for children positive on the mannitol challenge was 84 mg [CI: 26-266]. There was no significant correlation between the lowest dose of mannitol that provoked a cough response and logPD15 and log RDR to mannitol. 40% of children (n=9) had positive response on the exercise challenge test and 36%(n=9) were positive on both test and 44%(n=11) were negative for both tests. Positive predictive... |

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value of the mannitol for exercise-induced bronchoconstriction (EIB) was 69% and the negative predictive value was 91%. The mannitol challenge appears to be a suitable alternative for an exercise provocation test to assess EIB in asthmatic children. The mannitol challenge can be used as a screening tool to assess EIB. Giving the negative predictive value of 91%, it is especially useful to exclude EIB. It is a practical option because: it can be used as an office-based test, the equipments used are inexpensive, it is faster and easier to perform, it does not require specifically trained personnel or specialized equipments such as treadmills and/or dry air source, it can be used in disabled children because it does not need strenuous exercise or motor skills from the patient, and the test can be stopped before a severe drop in FEV1 happens.

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| Citation & Date                     | Study Design              | Age range              | # of patients | Intervention & Dose                                                                 | Comparison                                      | Outcomes considered                        | Benefits                                                                 | Side effects                                                                                   | Results/Comments                                                                                   |
|-----------------------------------|---------------------------|------------------------|---------------|---------------------------------------------------------------------------------|------------------------------------------------|---------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Subbarao 2000 Hospital for Sick Children, Toronto, Canada | observational prospective cohort | 6-13 years (only 2 were above our target population) | 35 (n=25 asthmatic children and n=10 non-asthmatic, healthy children) | Mannitol, dry powder, dose(0,5,10,20, 40,80,160,160, 160 mg) All subjects performed the Methacoline challenge test on the initial visit and the mannitol challenge test in the two subsequent visits either once(n=16) or twice(n=9) | Methacoline (concentrations not stated) | Forced expiratory volume in one second(FEV1) | Mannitol challenge was faster to perform than Methacoline. The mannitol challenge test identified asthmatic children in less than half the time of the Methacoline challenge test. Cough in one case after inhaling mannitol prevented completion of the challenge. False positive results with Methacoline challenge test(Non-asthmatic healthy children who did not respond to Methacoline did not respond to mannitol however, 30% of healthy children with no asthma history had a positive Methacoline challenge) | Cough in one case after inhaling mannitol prevented completion of the challenge. False positive results with Methacoline challenge test(Non-asthmatic healthy children who did not respond to Methacoline did not respond to mannitol however, 30% of healthy children with no asthma history had a positive Methacoline challenge) | Mannitol identifies children with airway hyperresponsiveness and is faster to perform than the Methacoline challenge. In 21 children with positive response to both tests, Geometric mean(GM)of provocative dose to produce a 15% fall in FEV1(PD15) for mannitol was 38.5mg(CI:19.1-77.8mg) and this compared with a provocative concentration to produce a 20% fall in FEV1(PC20) to Methacoline of 0.6 mg/mL(CI:0.35-1.02mg/mL). There was a significant relationship between the responses to mannitol and Methacoline challenge. There was good reliability of the PD15 result to mannitol and it was independent of dose. There was no significant difference between mannitol PD20 for the first challenge[41.6 mg(CI:25.9-66.9 mg)] compared with the |

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<td>second challenge [44.5 mg (CI: 26.5-74.8 mg) P=0.69]. There was no significant mean decrease in oxygen saturation during the challenges. The rate of spontaneous recovery to baseline FEV1 in asthmatic children was similar in mannitol and methacoline. There was no significant difference in final %fall in FEV1 after mannitol [26.6±6.5 % (mean±SD; range, 20.5-42.5%)] compared to methacoline [25.7±7.0 % (range, 20.0-43.8%; P=0.7, n=20)]. No child had a fall&gt;15-20% in FEV1 after a placebo dose. In non-asthmatic healthy children, the final fall in FEV1 to mannitol was 3.4±2.9 % (mean±SD; range 0-7.9%) after the maximum cumulative dose of 635 mg. This compared to a final %fall in FEV1 after methacoline of 6.8±4.7 % (mean±SD; range 0-14.1%).</td>
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<tr>
<td>Horsman 2009</td>
<td>observational prospective cohort</td>
<td>8-21 years</td>
<td>16/16</td>
<td>Mannitol, dose(0,5,10,20, 40,80,160,160, 160 mg)</td>
<td>None stated</td>
<td>FEV1</td>
<td>Mannitol challenge was well tolerated by all subjects. No subject requested to terminate the test due to discomfort. All subjects with positive challenges showed rapid reversibility of airflow obstruction and return to baseline lung function post bronchodilator</td>
<td>One subject complained of mild cheat tightness 30 min after completing the challenge. Upon two puffs of albuterol, this symptom was fully resolved.</td>
<td>4 subjects had negative response and 10 had positive response (8 had a ≥15% fall in FEV1 from baseline and 2 had a ≥10% fall in FEV1 between doses of mannitol). Subjects with positive challenge had a mean decrease in FEV1 of 18.4±5.9% and a mean increase in the resistance measurement at a frequency of 5 Hz (R5) of 34.8%±15% and there was no significant change in the resistance measurement at a frequency of 20 Hz. Subjects with negative challenge had no significant change in FEV1, R5, or R20. Assessment of airflow obstruction with mannitol challenge is a reliable alternative in patients that can not perform repeated spirometry.</td>
</tr>
<tr>
<td>Anderson 2009</td>
<td>Multi centre randomized controlled trial</td>
<td>6-50 years</td>
<td>509</td>
<td>Mannitol, dose(0,5,10,20, 40,80,160,160, 160)</td>
<td>Methacoline concentrations (0.0312, 0.0625, 0.125, 0.5,1,2,4,8,16 mg/mL)</td>
<td>Exercise-induced bronchoconstriction (EIB) as a manifestation of bronchial hyperresponsiveness</td>
<td>Not stated</td>
<td>None stated</td>
<td>The sensitivity and specificity of mannitol to identify EIB was 59%/65% and for Methacoline 56%/69%. Mean EIB % fall in FEV1 in subjects positive to exercise was 19% (SD 9.2), mannitol</td>
</tr>
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<td>PD15, 158(CI: 129,193) mg, and Methacoline pc20, 2.1(CI: 1.7, 2.6) mg/ml. The prevalence of bronchial hyperresponsiveness (BHR) was the same: for exercise (43.5%), mannitol (44.8%), and Methacoline (41.6%) with a test agreement between 62&amp;69%. The sensitivity and specificity for a clinician diagnosis of asthma was 56%/73% for mannitol and 51%/75% for Methacoline. The sensitivity increased to 73% and 72% for mannitol and Methacoline when the two tests were positive. Sensitivity and specificity were equivalent for mannitol and Methacoline to identify EIB and a clinical diagnosis of asthma.</td>
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Table 7: Mannitol use in Cystic Fibrosis

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<tbody>
<tr>
<td>Daviskas 2010 Royal Prince Alfred Hospital, Australia</td>
<td>Randomized double blind placebo controlled crossover study</td>
<td>&gt;8 years</td>
<td>28</td>
<td>Mannitol, inhale 420 mg twice a day for 2 weeks</td>
<td>Placebo</td>
<td>Sputum properties (solid content, wettability, rheology)</td>
<td>Regular treatment with inhaled mannitol increases the hydration and changes the surface properties favourably in patients with cystic fibrosis. These changes were sustained for 12 hours after the last treatment and correlated significantly with the improvement in lung function in response to inhaled mannitol</td>
<td>None stated</td>
<td>2 weeks treatment with mannitol reduced the solids from 7.3% ±3.0% to 5.7%±3.0%, surface tension from 83.1±7.2 to 78.6±8.0 mN/m, and contact angle from 52.4%±7.7 to 47.9%±7.3 degrees. Placebo treatment had no significant effect on sputum properties. The authors concluded that treatment with inhaled mannitol over 2 weeks improved the hydration and surface properties of sputum in patients with CF. This effect was sustained and correlated with airway function changes.</td>
</tr>
<tr>
<td>Jaques 2008 Several centers in Australia and New Zealand</td>
<td>Randomized double blind placebo controlled crossover study</td>
<td>8-48 years</td>
<td>39 (27 children less than or equal to 18 years of age)</td>
<td>Mannitol, 420 mg of dry powder for two weeks then crossed over to the placebo group after 2 weeks washout period</td>
<td>Placebo for two weeks then crossed over to the mannitol group after 2 weeks washout period</td>
<td>Lung function (FEV1, FVC, FEV1/FVC ratio, and peak expiratory flow rate)</td>
<td>7.0% mean relative increase in the FEV1 from baseline after treatment with Mannitol (significantly different from the 7 serious adverse events occurred during this study but none were considered to be treatment</td>
<td>None stated</td>
<td>Mannitol treatment increased FEV1 from baseline by a mean of 7.0%(95% CI: 3.3-10.7) compared to placebo. 0.3%(95%CI: -3.4-</td>
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<tbody>
<tr>
<td>Minasian 2009</td>
<td>Randomized trial (Open cross over study)</td>
<td>8-18 years</td>
<td>38 were recruited but 20 complete the study</td>
<td>Mannitol, dry powder, incrementally increasing doses of mannitol up to a maximum cumulative dose of 475 mg.</td>
<td>rhDNAse alone (2.5 mg) and combination of rhDNAse plus mannitol</td>
<td>FEV1, FVC (forced vital capacity), and FEF (forced expiratory flow)</td>
<td>3 months treatment with inhaled mannitol was as effective as rhDNAse and resulted in 7% increase in FEV1</td>
<td>change seen after the placebo) related and none resulted in death.</td>
<td>4.0). The absolute improvement with mannitol therapy was 121 mL (95%CI: 56.3-185.7), which was significantly more than that with placebo (0 mL, 95%CI: -64.7-64.7). The forced expiratory flow in the middle half of FVC increased by 15.5% (95%CI: -6.5-24.6) compared to that with placebo (increase, 0.7%. 95%CI: -8.3-9.7) This study concluded that inhaled mannitol treatment over a period of 2 weeks significantly improved lung function in patients with CF. Mannitol therapy was safe and well tolerated.</td>
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<tr>
<td>Hospital for Children NHS trust, UK</td>
<td>Observational study</td>
<td>8-17 years</td>
<td>39</td>
<td>Mannitol, dry powder, incrementally increasing doses of mannitol up to a maximum cumulative dose of 475 mg.</td>
<td>None stated</td>
<td>FEV1</td>
<td>24% of children with CF had a positive airway challenge with inhaled mannitol</td>
<td>Cough was common during challenge. Vomiting (n=2). Dizziness and chest tightness (n=1). One challenge was abandoned due to nausea.</td>
<td>9/38 subjects(24%, 95%CI:10-38%) had a positive challenge. Only 2/9 had a dose of mannitol required to cause a 15% reduction in FEV1(PD159 prior to the 315 mg dose, the remaining 7 children dropping their FEV1 by≥15% on the 315 or 475 mg final dose.</td>
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<td>cumulative dose. The authors concluded that 24% of children with CF had a positive airway challenge test with mannitol but they could not identify factors predictive of positive mannitol challenge in these children.</td>
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Table 8: Mannitol use in other indications

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<tr>
<td>Rigden 1984, Thoracic Unit, Hospital for Sick Children, UK</td>
<td>Randomized controlled trial</td>
<td>&gt;1 year</td>
<td>40</td>
<td>20% Mannitol solution, 0.5 g/kg</td>
<td>Hartmann's solution (Na 131, Cl 111, Ca 2, K 5, Lactate 29 mmol/l)</td>
<td>Renal function (by measuring plasma creatinine, albumine, and activity of N-acetyl-glucosaminidase)</td>
<td>Significant lower plasma creatinine concentrations and urinary albumine excretion rates</td>
<td>None stated</td>
<td>Lower plasma creatinine concentration and urinary albumine excretion rates in the treated compared to the control group. This study concludes that the result supports the hypothesis that mannitol can protect the kidney from ischemic damage sustained during periods of hypoperfusion. The children who received mannitol had a more rapid recovery of plasma creatinine postoperatively and less albuminuria.</td>
</tr>
<tr>
<td>Soriano 1996, Department of Anesthesia, Children's Hospital, Harvard Medical School, USA</td>
<td>Control trial (each patient was his or her own control)</td>
<td>1-14 years</td>
<td>10</td>
<td>Mannitol 1 g/kg over 15 minutes</td>
<td>Before and after mannitol infusion</td>
<td>Cerebral blood flow velocity (CBFV), Osmolality, hematocrite, mean arterial pressure, heart rate, and transcranial Doppler variables.</td>
<td>Increased osmolality, decreased hematocrite, increase in resistance distal to middle cerebral artery</td>
<td>None stated</td>
<td>Mannitol infusion resulted in an increase in osmolality and decrease in hematocrite (P&lt;0.05). Heart rate, MAP and arterial carbon dioxide tensions did not change (P&gt;0.05) during the measuring period. This study suggests that mannitol briefly increases cerebrovascular resistance and thereby diminishes cerebral blood volume.</td>
</tr>
<tr>
<td>Oommen 1980, University of Missouri, Columbia Medical Center</td>
<td>Prospective study</td>
<td>Neonate s</td>
<td>42</td>
<td>Mannitol, 1 g/kg</td>
<td>Saline 20 ml/kg</td>
<td>Urine out put (Oliguria to differentiate renal failure from pre-renal oliguria)</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Benefits if using mannitol as a diagnostic intervention not clear!</td>
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| USA  
Rando 2009 University hospital, Montevideo Uruguay | Descriptive retrospective study | <10 years old (3-144 months) | 107 | Mannitol, 0.25-0.5 g/kg | No mannitol | Hyponatremia | None stated | None stated | Severe, moderate, and mild intraoperative hyponatremia occurred in 14(13%), 21(19%), and 23(22%) children respectively. Mannitol was given to 31(29%) children but was not associated with the development of hyponatremia. Hyponatremia occurred frequently in children undergoing craniofacial surgery despite avoidance of low sodium solutions, and was unrelated to the administration of mannitol |
| USA  
Ruf 2003 University medical Center, Giessen, Germany | Case series | 5-11 years | 6 | Mannitol, 0.5 g/kg infusion in 15 minutes | Craniectomy | Neurological outcome | None stated | None stated | In all cases, ICP normalized after craniectomy. At discharge, 3 children were without disability, 2 children had a mild arm-focused hemiparesis, and one child had a spastic hemiparesis and verbal impairment. The spastic hemiparesis improved within 6 months and all others remained unchanged. In case of sustained increase in ICP(20mmHg) under intensified conservative therapy conditions and early decompressive craniectomy including duraplasty has to be considered There currently seems to be no specific treatment |
<table>
<thead>
<tr>
<th>Citation &amp; Date</th>
<th>Study Design</th>
<th>Age range</th>
<th># of patients</th>
<th>Intervention &amp; Dose</th>
<th>Comparison</th>
<th>Outcomes considered</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Results /Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daljit 2009</td>
<td>Case series</td>
<td>7-16 years</td>
<td>6</td>
<td>Mannitol 0.5-1 g/kg IV</td>
<td>No Mannitol</td>
<td>Intradialytic symptoms, hypotension or premature discontinuation of dialysis, percentage dry weight removed</td>
<td>Intradialytic mannitol significantly increased the mean treatment ultrafiltration volume. Mannitol halved the odds of Intradialytic symptoms and hypotension/ premature discontinuation of dialysis</td>
<td>None stated</td>
<td>Prophylactic use of mannitol reduces the Intradialytic symptoms and hypotension. Mannitol successfully treats milder degrees of disequilibrium, thus allowing treatments to proceed to completion. This study demonstrated the benefits of sequential dialysis, prophylactic mannitol and oral midodrine as viable rescue options, but these should not replace the fundamental issue of avoiding salt and water excess.</td>
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<tr>
<td>Lewis, 1999</td>
<td>Case series</td>
<td>4-9 years</td>
<td>3</td>
<td>20% Mannitol(5 ml/kg over one hour) and frusemide(2 mg/kg/dose) combination therapy(intravenous)</td>
<td>None stated</td>
<td>Loss of oedema</td>
<td>All 3 patients responded with loss of oedema</td>
<td>None stated</td>
<td>In normovolemic or hypervolemic patients with nephritic syndrome, Mannitol is safe and inexpensive treatment that allows for use more than once daily if needed. It will be of great value in developing countries where the availability and purity of 20% albumin is limited.</td>
</tr>
</tbody>
</table>

† Elevated intracranial pressure, intracranial hypertension, or cerebral oedema is used interchangeably along the text.