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[Intervention Review]

Fluid restriction for term infants with hypoxic-ischaemic encephalopathy following perinatal asphyxia

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ABSTRACT

Background

Current recommendations to control the consequences of hypoxic-ischaemic encephalopathy following perinatal asphyxia include the careful management of fluids, with avoidance of fluid overload and thus avoidance of cerebral oedema. Recommendations for fluid restriction in a neonate are based on the experience of restricting fluid intake in adults or older children. The extrapolation from studies in adults, older children and animals to the human neonate is fraught with hazard due to the different physiology and mechanisms of injury.

Objectives

The objective of this review was to determine the effects of fluid restriction on short-term (mortality within the first 28 days of life, grade of hypoxic ischaemic encephalopathy, electrolyte disturbances, renal function, seizure activity) and long-term outcomes (death during the first year of life, CT or MRI changes, or severe neurodevelopmental disability at or equal to 12 months of age or more) in term infants following perinatal asphyxia. Subgroup analyses were planned on the basis of the severity of the resulting hypoxic-ischaemic encephalopathy, degree of fluid restriction, and length of fluid restriction.

Search methods

Searches were undertaken of MEDLINE October 2004 back to 1966, CINAHL back to 1966, the Oxford Database of Perinatal Trials and the Cochrane Central Register of Controlled Trial (CENTRAL, The Cochrane Library, Issue 3, 2004). Searches were made of previous reviews including cross-references and abstracts. The search was not limited to the English language; reports in foreign languages were translated.

Selection criteria

Randomised or quasi-randomised trials of fluid restriction in term newborn infants with perinatal asphyxia.

Data collection and analysis

No studies were found meeting the criteria for inclusion in this review.

Main results

No studies were found meeting the criteria for inclusion in this review.

Fluid restriction for term infants with hypoxic-ischaemic encephalopathy following perinatal asphyxia (Review)

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Authors' conclusions

Given that fluid restriction for the treatment of hypoxic ischaemic encephalopathy following perinatal asphyxia is recommended in standard textbooks, there is a need for randomised, controlled trials to establish if this practice affects mortality and morbidity. As it may not be ethical to include neonates with acute renal failure in a randomised trial, these babies will have to be excluded from the trial. These studies should investigate the effects of fluid management on outcomes such as mortality, seizure activity, evidence of cerebral damage on histology, and effects on renal function and electrolytes.

PLAIN LANGUAGE SUMMARY

Fluid restriction for term infants with hypoxic-ischaemic encephalopathy following perinatal asphyxia

Plain language summary will be included with future review update.

BACKGROUND

Despite advances in biophysical and biochemical monitoring of the fetus in labour and during delivery, perinatal asphyxia and associated hypoxic ischaemic encephalopathy (HIE) remain an important cause of perinatally acquired brain damage in term infants, with an incidence of 2-9 per 1000 babies (Gomella 1999). Generally, the treatment of the infant with HIE is supportive. However, very few of the commonly employed methods for managing asphyxiated infants have actually been tested in controlled clinical studies and most of these remain ineffective in controlling the consequences of HIE (Sinha 1998). Many organs can be affected by a hypoxic-ischaemic injury. Apart from cardiac compromise and hepatic dysfunction, the most commonly seen symptoms are those of cerebral oedema, compromised renal function and the syndrome of inappropriate antidiuretic hormone secretion. Current recommendations to control the consequences of hypoxic-ischaemic encephalopathy (HIE) include the careful management of fluids, with avoidance of fluid overload with the hope of avoiding cerebral oedema. Consequently, fluid restriction is one of the most common treatment modalities for HIE (Donn 1986, Gomella 1999, Levene 2000, Fedorova 1982). However, the unique body fluid composition of the neonate and the presence of central nervous system (CNS) injury and compromised renal function following HIE make calculation of appropriate fluid management difficult. Extreme fluid restriction can lead to dehydration and hypotension, resulting in decreased cerebral perfusion, which may lead to adverse neurological outcome.

In term infants, about 75% of body weight at birth is made up by water (Dweck 1975). Weight loss in the first week of life is the result of a decrease of extracellular fluid via diuresis and a negative fluid balance. The calculation of fluid requirements must take into

consideration the maintenance needs, losses and possible deficits. Therefore the difference between fluid losses, including urine production, insensible losses from the skin and lungs, and stool losses, and fluid intake from feeds or parenteral fluids needs to be carefully considered in order to avoid dehydration or overhydration. In the well term infant, fluid requirements in the first few days vary depending on the level of maturity, environmental temperature, body temperature and ambient humidity. Maintenance fluid requirements in these babies range from 60 to 120 ml/kg/d in the first three days (Beischer 1997).

The rationale for fluid restriction following perinatal asphyxia is the avoidance of fluid overload and the exacerbation of cerebral oedema. Cerebral oedema may occur as a result of a hypoxic-ischaemic insult. Klatzo defined two forms of cerebral oedema: 1. vasogenic oedema as a result of increased permeability of the blood brain barrier; 2. cytotoxic oedema manifested as intracellular swelling without increased permeability of the blood brain barrier (Klatzo 1967). It now seems evident that cytotoxic rather than vasogenic oedema may occur as a result of ischaemia (Kimmelberg 1995). Increased intracranial pressure (ICP) does not introduce any acute functional neurological disturbances (Clancy 1988). Animal studies of hypoxia-ischaemia also do not support the view that cerebral oedema is a primary injury causing further cerebral insult, but is rather a consequence of the ischaemic damage in the immature animal (De Haan 1997, Muijsce 1990, Stonestreet 1992).

In current clinical practice, restriction of maintenance fluid intake to anywhere between 40 to 70 ml/kg/day is recommended for neonates with HIE (Levene 2000, Gomella 1999). These recommendations are based on experience from the treatment of adults

and children (Shenkin 1976, Yu 2000), or from animal models of cerebral hypoxia and/or ischaemia (Morse 1985). In adults and children, fluid restriction is commonly used in the brain injured patient (Shenkin 1976) and post-resuscitation from cardiac arrest (Hao-Hui 1980). In a series of cases using three different levels of fluid intake (Shenkin 1976) in 30 adult patients, it was found that fluid restriction (1055 ml/day) maintained the patients in a homeostatic balance. A larger fluid intake caused a decrease in serum osmolality with only minor changes in urea nitrogen and hematocrit, indicating expansion of extracellular space with the potential to worsen cerebral oedema. However, in an adult rat model of experimentally induced cerebral oedema, hydration status did not influence the extent of cerebral oedema (Morse 1985). Neither study provided assessment of either short term or long-term neurological function. A significant decrease in mortality (from 63.5% to 17.2%) was found in a study comparing fluid intake of 60 ml/kg/day with an individualised approach to fluid therapy (40-208 ml/kg/d) in 3773 children aged 1 day to 13 years (Yu 2000). However, no comment was made in regards to aetiology or long-term outcome other than mortality in these children. There was also no mention of the effects on children of different age groups. Although the recommendations for fluid restriction in a neonate are based on the experience of restricting fluid intake in adults or older children, one has to keep in mind that the maintenance fluid requirement in neonates per kg bodyweight is much higher than in older children and adults. Quantitative recommendations for fluid restriction in neonates cannot be derived from the above-mentioned studies. The extrapolation from studies in adults, older children and animals to the human neonate is fraught with hazard due to the different physiology and mechanisms of injury.

The predictive value of clinical signs at or after birth, such as Apgar scores, cord pH, or clinical symptoms of encephalopathy, is low. Ultrasound has a low sensitivity in term babies with HIE. Only if cystic lesions are detected does it show a good correlation with spastic diplegia (Siegel 1984, de Vries 1985). CT can demonstrate diffuse cerebral oedema (Volpe 2000), injury to the cortex and white matter, and damage to central grey matter structures such as thalamus and basal ganglia (Roland 1998). MRI is superior to ultrasound and CT in assessing maturational changes because of its better visualisation of myelination and structural changes (Martin 1995). MRI is a useful tool in evaluating the extent of brain damage within the first 10 days of birth (Barkovich 1995) and is often used in conjunction with neurological assessment for prognostication of outcome.

OBJECTIVES

The objective of this review was to determine the effects of fluid restriction on short-term (mortality within the first 28 days of life, grade of hypoxic ischaemic encephalopathy, electrolyte distur-

bances, renal function, seizure activity) and long-term outcomes (death during the first year of life, CT or MRI changes, or severe neurodevelopmental disability at or equal to 12 months of age or more) in term infants following perinatal asphyxia. Subgroup analyses were planned on the basis of:

- i. severity of asphyxia (HIE grade 1, 2, or 3) (Sarnat 1976)
- ii. degree of fluid restriction (50-59 ml/kg/day; < 50 ml/kg/day, no fluid restriction)
- iii. length of fluid restriction (1 day, 1-3 days, > 3 days)

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials.

Types of participants

Neonates of 37 or more weeks completed gestation and less than three days postnatal age following perinatal asphyxia. Participants must fulfil the criteria for perinatal asphyxia as defined jointly by the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG):

1. metabolic or mixed acidaemia (pH <7.0) on umbilical cord gas sampling if obtained
2. an Apgar score of 0 to 3 for more than five minutes
3. neonatal neurologic complications, e.g. seizures, coma or hypotonia; and
4. multisystem organ dysfunction, e.g. cardiovascular, hematologic, pulmonary, or renal system.

Types of interventions

The intervention was restriction of maintenance fluid intake to < 60 ml/kg/day administered within the first three days of life with the aim to prevent neuronal injury following perinatal asphyxia. This intervention was compared with infants who did not have fluid restriction (fluid intake >60 ml/kg/day). Fluids given for resuscitation, such as colloid or blood, will not be included in the fluid calculation.

Types of outcome measures

Primary outcomes:

- Neonatal mortality (death during the first 28 days of life)
- Infant mortality (death during the first year of life)

Severe neurodevelopmental disability at or equal to 12 months of age or more. Severe neurodevelopmental disability was defined as: cerebral palsy, developmental delay (DQ <70) or blindness (visual acuity < 6/60 in both eyes), or any combination of these disabilities.

Secondary outcomes:

Hypoxic ischaemic encephalopathy, highest grade ([Sarnat 1976](#))

Electrolyte disturbances:

- a) Hyponatraemia (serum sodium concentration <130 mmol/L) or hypernatraemia (serum sodium concentration > 150 mmol/L)
- b) Hypokalaemia (serum potassium concentration < 3 mEq/L) or hyperkalaemia (serum potassium concentration > 7 mEq/L)

The measurements were recorded within the first 24 hours of life as a reflection of the asphyxial insult and compared with measurements made at least 24 hours after the initiation of the therapy (result of the therapy).

Urine output (oliguria defined as urine output < 1 ml/kg/h) during the first three days of life. The measurements were recorded within the first 24 hours of life as a reflection of the asphyxial insult and compared with measurements made at least 24 hours after the initiation of the therapy (result of the therapy).

Renal function (renal failure defined as serum creatinine > or = 1.5 mg/dL/133 micromol/L). The measurements were recorded within the first 24 hours of life as a reflection of the asphyxial insult and compared with measurements made at least 24 hours after the initiation of the therapy (result of the therapy).

Seizure activity (detection of seizures based on either clinical grounds, detection by electroencephalogram, or by treatment of seizures with antiepileptic treatment).

CT or MRI changes consistent with asphyxia.

Search methods for identification of studies

See: Cochrane Neonatal Review Group search strategy.

Searches were undertaken of MEDLINE July 2004 back to 1966, CINAHL back to 1966, the Oxford Database of Perinatal Trials and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2004) using the following terms:

infant, newborn (explode) [MeSH heading],
asphyxia (explode), [MeSH heading],
fluid therapy [MeSH heading],
ischaemia/ischemia (textword)
hypoxia (textword)
encephalopathy (explode) [MeSH heading]

Searches were made of previous reviews including cross-references and abstracts. The search was not limited to the English language; reports in foreign languages were translated. The title and abstract of each review were assessed for eligibility. If there was uncertainty, the full report was reviewed.

Data collection and analysis

Criteria and methods used to assess the methodological quality of the trials are the standard methods of the Cochrane Collaboration and the Neonatal Review Group.

All review authors searched for studies for the review. All review authors assessed eligibility for inclusion of the review. Studies were assessed using the following key criteria: blinding of randomisation, blinding of intervention, completeness of follow-up and blinding of outcome measurement. Differences were resolved by discussion and consensus of the review authors.

Weighted mean differences (and 95% confidence intervals) were to be reported for continuous variables such as duration of seizures. For categorical outcomes such as mortality, the relative risk (and 95% confidence intervals) and risk difference (and 95% confidence intervals) were to be reported. We were to use a fixed effect-model for meta-analysis and the heterogeneity statistic to help decide whether pooling was justified.

RESULTS

Description of studies

The search identified one paper that required translation ([Fedorova 1982](#)). After translation, we found this to be a review article, therefore it was not included in the review. No trials were found that addressed the use of fluid restriction following perinatal asphyxia. Subsequently, no studies were found meeting the criteria for inclusion in this review.

Risk of bias in included studies

No studies were found meeting the criteria for inclusion in this review.

Effects of interventions

No studies were found meeting the criteria for inclusion in this review.

DISCUSSION

Given that we found no randomised controlled trials that address the use of fluid restriction following perinatal asphyxia, this systematic review does not establish if fluid restriction reduces mortality and morbidity.

A strength of the review is the fact that the search strategy was broad and comprehensive. Using a broad definition of asphyxia and then combining this with fluid therapy or encephalopathy allowed us to search as widely as possible. All abstracts were reviewed by the authors and the full report read and examined if there was uncertainty about the abstract. Only review articles or recommendations for the treatment of perinatal asphyxia were found by using this search strategy. Missing publications before 1966 is a weakness of the review, especially if one considers that randomisation of acutely ill (i.e. babies in renal failure) babies may have been done then but may not be considered to be ethical today.

Although most standard texts recommend fluid restriction as a treatment of neonates with HIE, it is obvious that these recommendations are not based on evidence from randomised controlled trials in neonates. They are much more likely to be based on evidence from adult studies. Avoiding fluid overload as a result of the renal dysfunction frequently seen after perinatal asphyxia will also play a role in current recommendations. However, the question remains why there are no randomised trials in neonates comparing fluid restriction with no fluid restriction. Reluctance to randomise severely asphyxiated infants to non-restricted fluids with the risk of worsening cerebral outcome may be the reason that no trials have been conducted. Renal dysfunction caused by perinatal asphyxia necessitates the restriction of fluids and, therefore, enrolling babies with renal failure into a randomised trial may not be ethical. If cerebral oedema is the consequence, rather than the cause of perinatal brain injury, then reduction of cerebral oedema will have little effect on neurological outcome. Supporting this observation, pharmacological manipulation of oedema has not been shown in animal studies to affect neuropathological outcome, despite decreasing the level of cerebral oedema by up to 70% (Vannucci 1993). However, one has to keep in mind that even if reduction of cerebral oedema may not affect neurological outcome, an increase in cerebral oedema to a degree that the compliant mechanisms of a neonatal skull are exhausted will result in an increase of the intracranial pressure and potentially contribute to cerebral damage.

Given the potential risk of worsening outcome, randomised studies in neonates may therefore not be ethical in all asphyxiated babies. However, current recommendations include all grades of HIE. Although fluid restriction may be beneficial for babies with

multiorgan damage and severe HIE, this is not necessarily the case for babies with a milder degree of HIE without renal failure. 25% of all babies with HIE II will have an adverse neurodevelopmental outcome. These babies do not necessarily have signs of multiorgan damage and may not be as severely compromised at birth as babies with HIE III. It is unclear if in those babies fluid restriction is beneficial. These babies with HIE II are the ones that should be included in a randomised trial. These studies should investigate the effects of fluid management on outcomes such as mortality, seizure activity, evidence of cerebral damage on histology, and effects on renal function and electrolytes.

AUTHORS' CONCLUSIONS

Implications for practice

We found no evidence from randomised, controlled trials to support or refute that the practice of fluid restriction in neonates following perinatal asphyxia affects mortality and morbidity.

Implications for research

Given that fluid restriction for the treatment of hypoxic ischaemic encephalopathy following perinatal asphyxia is recommended in standard textbooks, there is a need for randomised, controlled trials to establish if this practice affects mortality and morbidity. The most appropriate population group for these randomised trials are babies with HIE II. For babies with acute renal failure, animal models of hypoxia-ischaemia can be used to investigate the effects of fluid restriction, as it may not be ethical to include these babies in a randomised trial. These studies should investigate the effects of fluid management on outcomes such as mortality, seizure activity, evidence of cerebral damage on histology, and effects on renal function and electrolytes.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

WHAT'S NEW

Date	Event	Description
21 October 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 3, 2005

Date	Event	Description
31 March 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

GH and AJ wrote the background, with ZK contributing to the clinical aspects of HIE. ZK wrote the criteria for study inclusion and methods of the review.

All reviewers searched for studies to be included in the review. ZK wrote the recommendations for clinical practice.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Department of Neonatology, The Canberra Hospital, Australia.
- Cecilia Kilkerry Foundation, Australia.
- National Health and Medical Research Council, Australia.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Fluid Therapy; Asphyxia Neonatorum [*complications]; Brain Edema [prevention & control]; Hypoxia-Ischemia, Brain [etiology; *therapy]

MeSH check words

Humans; Infant, Newborn