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[Intervention Review]

Rapid correction of early metabolic acidaemia in comparison with placebo, no intervention or slow correction in LBW infants

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zsuzsoka.kecsek@act.gov.au.**Editorial group:** Cochrane Neonatal Group.**Publication status and date:** Edited (no change to conclusions), published in Issue 1, 2010.**Citation:** Kecskes Z, Davies MW. Rapid correction of early metabolic acidaemia in comparison with placebo, no intervention or slow correction in LBW infants. *Cochrane Database of Systematic Reviews* 2002, Issue 1. Art. No.: CD002976. DOI: [10.1002/14651858.CD002976](https://doi.org/10.1002/14651858.CD002976).

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ABSTRACT

Background

Metabolic or mixed (metabolic and respiratory) acidosis are commonly encountered problems in the low birth weight (LBW) infant after delivery, and they may contribute to mortality and morbidity. Causes for the lactic acidosis are multiple and include maternal, placental and fetal factors. It is unclear whether metabolic acidaemia in the first 24 hours of life in LBW infants should be corrected by rapid infusion of alkali.

Objectives

The main objective was to assess the short and long-term effects of the rapid correction of early (first 24 hours) metabolic acidaemia in LBW (<2500g birth weight) neonates.

Search methods

Searches were undertaken of MEDLINE from February 2004 back to 1966 and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2004). The title and abstract of each retrieved study were examined to assess eligibility. If there was uncertainty, the full paper was examined.

Selection criteria

Types of studies

All randomised controlled trials where short or long term effects of treatment with alkalisating agents by rapid infusion were compared with placebo or no treatment, or where rapid infusion of alkalisating agents was compared with slow infusion.

Types of participants

Newborn infants with birth weight <2500g and less than 24 hours of age with proven metabolic acidaemia (on arterial blood gas).

Types of interventions

Rapid correction of acidaemia with alkalisating agents (sodium bicarbonate and/or THAM) given as a bolus over 5 minutes or less compared with either placebo, no intervention or slow infusion (>5 minutes).

Types of outcome measures

- 1) maximal oxygen requirement in first 24 hours
- 2) duration of oxygen therapy
- 3) need for and duration of assisted ventilation

- 4) intraventricular haemorrhage and/or periventricular leucomalacia
- 5) survival to discharge
- 6) long term survival (to 24 months of age)
- 7) neurological and developmental outcome at 24 months of age

Data collection and analysis

Each reviewer assessed eligibility, trial quality and extracted data separately, then compared and resolved differences. Study authors were contacted for additional information if necessary.

Main results

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

Authors' conclusions

There is no evidence available from randomised controlled trials to support or refute the rapid correction of metabolic acidaemia, in LBW infants in the first 24 hours of life, as compared with slow or no correction.

PLAIN LANGUAGE SUMMARY**Rapid correction of early metabolic acidaemia in comparison with placebo, no intervention or slow correction in LBW infants**

Plain language summary will be included with future update.

BACKGROUND

Metabolic or mixed (metabolic and respiratory) acidosis are commonly encountered problems in the low birth weight (LBW) infant after delivery, and they may contribute to mortality and morbidity. Lactic acid is the product of anaerobic metabolism which occurs with perinatal asphyxia and/or hypoxaemia occurring during or after birth. Causes for the lactic acidosis are multiple and include maternal, placental and fetal factors.

Following hypoxaemia, cardiovascular, metabolic and behavioural responses occur which decrease oxygen demand and redistribute available oxygen to the brain, heart and adrenal glands. The consequences of these responses include vasoconstriction, inhibition of spinal reflexes, midbrain activation and increased sympathetic tone. A shift to the anaerobic metabolic pathway leads to an accumulation of lactic acid. The resulting acidaemia causes a right shift in the haemoglobin-O₂ dissociation curve which further lowers blood oxygen content. Hypoxaemia and acidosis also contribute to a high pulmonary vascular resistance which results in a right to left shunt. Right to left shunts have been demonstrated in infants born with perinatal asphyxia and respiratory distress syndrome.

Treatments for metabolic acidaemia include the use of alkalinising agents such as sodium bicarbonate or tromethamine (THAM), and oxygen. The purported benefits of normalising the pH include a reduction in pulmonary vascular resistance, an increase in myocardial contractility, improved hemodynamic responses to resuscitation with epinephrine and oxygen, and increased survival (Martin 1993; Preziosi 1993). However, evidence from randomised controlled studies in human infants does not support the use of sodium bicarbonate to improve mortality or incidence of intraventricular haemorrhage.

Several studies have raised doubt concerning the benefits of using alkalinising agents during hypoxic lactic acidosis. Although sodium bicarbonate corrects metabolic acidosis, its administration can lead to a transient decrease in intra-myocardial pH, cardiac output and blood pressure (Graf 1985; Kette 1990). The reason for this is that correction of metabolic acidosis with an alkalinising agent such as bicarbonate depends on the removal of CO₂ and only functions in an 'open' system (Ostrea 1972). This is according to the Henderson-Hasselbalch equation:

$$H^+ + HCO_3^- \rightleftharpoons H_2O + CO_2.$$

Small, stressed babies frequently accumulate CO₂ secondary to respiratory failure (Baum 1975). CO₂ crosses the cellular membrane very quickly and thus leads to worsening of intracellular acidosis by shifting the Henderson-Hasselbalch equation to the left. In addition to this, the administration of a hyperosmolar solution such as sodium bicarbonate causes changes in serum osmolality. The resulting fluid shift causes cells, including red blood cells, to lose water-increasing intracellular ionic strength (Ostrea 1972). Proteins then become stronger acids and generate additional acid by releasing protons (Howell 1987). There is also evidence that especially rapid injection (five minutes or less) of hypertonic solutions of sodium bicarbonate or THAM may be harmful. Rapid injection may cause increases in intra-vascular volume and venous pressure with profound effects on the brain including haemorrhage or haemorrhagic infarction (Finberg 1977). On the other hand, studies have shown an association between metabolic acidosis

and poor neurodevelopmental outcome (Goldstein 1995, Skouteli 1988).

The dilemma remains, therefore, of whether metabolic acidaemia in the first 24 hours of life in LBW infants should be corrected by rapid infusion of alkali. Our aim is to review the evidence concerning the use of rapid infusion (five minutes or less) of alkalinising agents to treat early (first 24 hours) metabolic acidaemia in LBW infants.

OBJECTIVES

The main objective was to assess the short-term (such as improved oxygenation as measured by blood gas analysis, oxygen requirement, length of ventilation, intracranial haemorrhage and neonatal survival) and long-term (such as survival and neurodevelopmental outcome) effects of the rapid correction of early (first 24 hours) metabolic acidaemia in LBW (<2500g birth weight) neonates.

The two comparisons therefore were:

1. rapid correction vs placebo or nothing
2. rapid vs slow correction

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials where short or long term effects of treatment with alkalinising agents by rapid infusion were compared with placebo or no treatment, or where rapid infusion of alkalinising agents was compared with slow infusion.

Types of participants

Newborn infants with birth weight <2500g and less than 24 hours of age with proven metabolic acidaemia on arterial blood gas. Metabolic acidaemia was defined as pH <7.25 with a PaCO₂ of <45 mm Hg.

Types of interventions

Rapid correction (bolus or rapid infusion over 5 minutes or less) of early metabolic acidaemia using sodium bicarbonate or THAM was compared with either: 1) placebo or no correction or 2) a slow infusion (> 5 minutes) of alkali.

Types of outcome measures

- 1) maximal oxygen requirement in first 24 hours
- 2) duration of oxygen therapy (hours or days)
- 3) need for and duration of assisted ventilation (intermittent positive pressure mechanical ventilation provided via a endotracheal tube) (hours or days)
- 4) intraventricular haemorrhage and/or periventricular leucomalacia (IVH/PVL)
- 5) survival to discharge
- 6) long term survival (to 24 months of age)
- 7) neurological and developmental outcome at 24 months of age

Search methods for identification of studies

Searches were undertaken of MEDLINE from February 2004 back to 1966 and the Cochrane Central Register of Controlled Trials

(CENTRAL, The Cochrane Library, Issue 1, 2004) using the following terms:

infant, newborn (explode) [MeSH heading],
acidosis [MeSH heading], acidaemia/acidemia [textwords],
sodium bicarbonate [MeSH heading],
THAM/tromethamine/Tris [textwords].

The title and abstract of each retrieved study was examined to assess eligibility. If there was uncertainty, the full paper was examined.

Data collection and analysis

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

Studies were assessed using the following key criteria: blinding of randomisation, blinding of intervention, completeness of follow up and blinding of outcome measurement. Data were extracted independently by the reviewers. Differences were resolved by discussion and consensus of the reviewers. If necessary, investigators were contacted for additional information or data. Weighted mean differences (and 95% confidence intervals) were to be reported for continuous variables such as duration of oxygen therapy. 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 the meta-analysis.

RESULTS

Description of studies

Five studies using sodium bicarbonate or THAM for correction of acidosis in low birth weight infants were identified. None were found to meet the criteria for inclusion in this review.

[Sinclair 1968](#) randomised 20 infants with a birth weight of 1000-2500g to receive one of four different treatment combinations which consisted of limited/unlimited environmental oxygen, slow/rapid bicarbonate administration and assisted/self-ventilation. Neonates admitted for the study had to be hypoxaemic ($pO_2 \leq 75$ in 50% headbox oxygen) and acidaemic ($pH \leq 7.25$ if under 4 hours of age but if older than 4 hours could be either). This study was excluded because the included babies had a mixed rather than a purely metabolic acidaemia.

[Van Vliet 1973](#) enrolled 50 newborn infants with severe respiratory distress (clinical signs and symptoms, typical chest x-ray and $PaO_2 < 100$ in 90 to 100% environmental oxygen) to receive either sodium bicarbonate or THAM. Although acidaemia was not necessary to be enrolled in the study, mean pH was 7.16. Method of randomisation was not described. This study was excluded because of the unclear randomisation, enrolment of neonates with birth weights $> 2500g$ and lack of acidaemia as an entry criteria for the study.

[Baum 1975](#) enrolled 19 neonates with severe respiratory distress into a non-randomised study to receive either a rapid (< 30 seconds) THAM injection or one of three sodium bicarbonate treatments (injection over 30 seconds, 2 minutes or 5 minutes). Acidaemia was not an entry criterion. Other reasons for exclusion were non-

randomisation and enrolment of neonates with birth weights $> 2500g$.

[Bland 1976](#) examined the effects of infusions of sodium bicarbonate over 5 to 10 minutes as compared with infusions of glucose or albumin in 51 hypoproteinaemic premature (< 37 weeks gestation) infants at risk of developing acidaemia. Acidaemia while present in the majority of infants was not an essential prerequisite for entry in this trial. This study was excluded because the infusion of sodium bicarbonate was longer than 5 minutes and because of the enrolment of newborn infants with birth weights $> 2500g$.

[Corbet 1977](#) studied the effects of a slow infusion of sodium bicarbonate in 62 acidaemic premature neonates with birth weights $< 1500g$ as compared with no treatment. Acidaemia while present in the majority of infants was not an essential prerequisite for entry in this trial. This study was excluded because it compared a slow infusion of sodium bicarbonate titrated to pH with no sodium bicarbonate.

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

There are no randomised controlled trials to support or refute the rapid correction of acidosis in LBW neonates with early metabolic acidosis.

We asked a very specific question about the use of rapid correction of metabolic acidosis, as opposed to slow or no correction, because of the concerns with regard to rapid infusion of alkalisating agents, especially in LBW infants. Observational studies in human newborn infants have reported an association between intraventricular haemorrhage and rapid injection of alkalisating agents ([Finberg 1977](#), [Simmons 1974](#)). This association is possibly due to the immediate effects of an injection of alkali such as hypernatremia, hyperosmolality or alterations of cerebral blood flow.

Studies on the immediate effects of an injection of sodium bicarbonate with hypernatremia and hyperosmolality include:

1. Simmons et al ([Simmons 1974](#)) - a comparison of two different approaches to correction of metabolic acidosis in human newborn infants with sodium bicarbonate in a retrospective review. He found that intracranial haemorrhage was associated with hypernatremia (> 150 mEq/L) or excessive sodium administration (> 8 mEq/kg/d) in 81% of the cases.
2. Papile et al ([Papile 1978](#)), in an observational study on the effect of sodium bicarbonate administration on intraventricular haemorrhage in very low birth weight infants, found no association between the serum sodium concentrations or amount of intravenous sodium bicarbonate administered and the occurrence of intraventricular haemorrhage. However they did find an association between a rapid infusion rate as well as high osmolality of sodium bicarbonate and intraventricular haemorrhage.

3. Finberg 1977 (Finberg 1977) also demonstrated that intraventricular haemorrhage is associated with the high concentration and rapid rate of infusion of sodium bicarbonate.

Others have investigated the immediate effects of an injection of sodium bicarbonate on cerebral blood flow. These include:

1. Lou et al (Lou 1978), who found a reduction of cerebral blood flow in human infants of up to 87% after variable doses of sodium bicarbonate (between 1 and 8 mEq/kg).
2. Laptook (Laptook 1985), who examined the effects of a moderate dose of sodium bicarbonate (2 mEq/kg infused over 3 minutes) on cerebral blood flow in a model using 1 day old piglets. He found no effect of sodium bicarbonate on cerebral blood flow or oxygen delivery if administered after hypoxia and acidaemia - however the dose used did not result in any alteration in osmolality or serum sodium concentrations.

Furthermore, other animal studies suggest there are other adverse effects with the correction of acidosis with alkalisating agents that may be harmful to the LBW infant.

1. Steichen and Kleinman (Steichen 1977) found that an infusion of sodium bicarbonate (2 mEq/kg infused over 3 minutes), in newborn dogs with fixed ventilation, increased serum osmolality and PaCO₂.
2. Graf et al (Graf 1985) showed that treatment of hypoxic lactic acidosis with sodium bicarbonate in dogs decreased cardiac output and blood pressure (Graf 1985).
3. Bureau et al (Bureau 1980) showed that correction of metabolic acidosis worsened cerebral hypoxia and cerebral acidaemia in dogs (Bureau 1980).

The other agent used to correct metabolic acidosis, THAM, also has concerns with regard to its use in sick LBW infants. THAM can cause depression of ventilation and hypoglycaemia, and delivers an even greater osmolar load than sodium bicarbonate (Heird 1972).

There are only two randomised controlled trials where alkali has been compared with placebo or no treatment in human infants who are acidaemic or at risk of acidaemia. A randomised trial by Corbet et al (Corbet 1977) comparing slow correction of acidaemia with no correction in preterm infants showed no benefit in terms of the rate of pH-correction, mortality or incidence of intraventricular haemorrhage. Bland et al (Bland 1976) performed a randomised controlled trial comparing two doses of sodium bicarbonate with albumin or dextrose-water infused over 5-10 minutes in infants at risk of acidaemia (hypoproteinaemic and less than 37 weeks

gestation) within two hours of birth - there were no differences in mortality, intracranial haemorrhage or the incidence of respiratory distress syndrome. There was a trend to increased mortality and incidence of intracranial haemorrhage in the groups treated with sodium bicarbonate. There seems to be little available evidence supporting the correction of metabolic acidaemia by any means.

Because the effects of rapid injection of alkali, described above, can have an effect on neurodevelopmental outcome these worrisome reports should lead the clinician to caution. In the absence of any evidence of benefit from the rapid injection of alkali it would be difficult to justify its use in LBW infants with metabolic acidosis.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence available from randomised controlled trials to support or refute the rapid correction of metabolic acidosis, in LBW infants with metabolic acidosis in the first 24 hours of life, as compared with slow or no correction.

Implications for research

If rapid correction is thought to be a useful treatment in the correction of metabolic acidaemia then there is a need for studies, with a larger number of infants, to clarify whether there is any benefit from this treatment without significant harm. However, given the lack of evidence that any correction of metabolic acidaemia confers significant benefit without harm, it would probably be prudent to investigate whether any correction of metabolic acidaemia is beneficial before studying rapid correction. Any studies investigating the use of alkalisating agents should include important clinical outcomes such as ventilatory parameters, mortality, IVH/PVL and neurodevelopmental outcome. Despite the apparent lack of benefit or detriment of rapid correction of metabolic acidosis, the potential hazards of this therapy should be appreciated. As caution is warranted as to the possibility of intraventricular bleeding after rapid injection of alkalisating agents, this question may best be answered in animal studies first.

ACKNOWLEDGEMENTS

Thanks to Dr Adrian Ziino for the translation of the Italian language articles and Dr Luis Altamirano for the translation of a Spanish language article.

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Steichen 1977

Steichen JJ, Kleinman LI. Studies in acid-base balance: Effect of alkali therapy in newborn dogs with mechanically fixed ventilation. *Journal of Pediatrics* 1977;**91**:287-91.

References to other published versions of this review

Kecskes 2002

Kecskes ZB, Davies MW. Rapid correction of metabolic acidaemia in comparison with placebo, no intervention or slow

correction in VLBW infants. *Cochrane Database of Systematic Reviews* 2002, Issue 1. [DOI: [10.1002/14651858.CD002976](https://doi.org/10.1002/14651858.CD002976)]

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Baum 1975	Not randomised; two forms of treatment compared with each other (THAM in ventilated infants, sodium bicarbonate for non-ventilated infants).
Bland 1976	Infants included were hypoproteinaemic and <37 weeks gestational age, no birthweight cut-off; trial compares slow infusion with albumin and placebo.
Corbet 1977	Comparison of slow infusion of sodium bicarbonate titrated to pH with no sodium bicarbonate.
Sinclair 1968	The study participants did not all have "proven metabolic acidaemia (on arterial blood gas)" at enrolment into the study.
Van Vliet 1973	All babies with severe RDS were randomly treated with either sodium bicarbonate or THAM. Randomisation method is unclear, method of application of initial dose of buffer not reported.

WHAT'S NEW

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

HISTORY

Protocol first published: Issue 1, 2001

Review first published: Issue 1, 2002

Date	Event	Description
12 March 2004	New search has been performed	This review updates the existing review of "Rapid correction of early metabolic acidaemia in comparison with placebo, no intervention or slow correction in LBW infants", published in The Cochrane Library, Issue 1, 2002 (Kecskes 2002). No new trials have been identified as a result of the most recent search and no changes have been made to this review.
8 October 2001	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

ZBK - wrote the review, searched for references to include in the review, translated german, norwegian and french language articles, assessed the methodological quality of the trials considered for this review.

MWD - revised and edited the review, searched for references to include in the review, assessed the methodological quality of the trials considered for this review.

DECLARATIONS OF INTEREST

none

SOURCES OF SUPPORT

Internal sources

- Royal Children's Hospital Foundation, Royal Children's Hospital, Brisbane, Queensland, Australia.
- Perinatal Research Centre, Royal Women's Hospital, Brisbane, Australia.
- Dept of Paediatrics and Child Health, University of Queensland, Brisbane, Australia.
- Royal Women's Hospital, Brisbane, Australia.
- Cochrane Perinatal Team, Brisbane, Australia.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant, Low Birth Weight; Acidosis [*therapy]; Acidosis, Respiratory [therapy]; Buffers; Hydrogen-Ion Concentration; Sodium Bicarbonate [therapeutic use]; Tromethamine [therapeutic use]

MeSH check words

Humans; Infant, Newborn