Sodium bicarbonate infusion during resuscitation of infants at birth (Review)

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[Intervention Review]

Sodium bicarbonate infusion during resuscitation of infants at birth

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ABSTRACT

Background

For many years, intravenous sodium bicarbonate has been used to reverse acidosis during newborn resuscitation. However, controversy surrounds its use. Most of the evidence has been derived from studies in animals, adult humans, or in uncontrolled, descriptive experiments. Despite the lack of evidence from the human neonatal population and concerns about its safety, some international resuscitation guidelines still recommend the use of sodium bicarbonate in resuscitation of the newborn.

Objectives

To determine whether an intravenous infusion of sodium bicarbonate, compared to placebo or no treatment, reduces mortality and morbidity (in particular regarding neurodevelopmental outcome) in infants receiving resuscitation in the delivery room at birth.

Search strategy

We used the standard search strategy of the Cochrane Neonatal Review Group. Searches were conducted of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 3, 2005), MEDLINE (1966 - September 2005), EMBASE (1980 - September 2005) and CINAHL (1982 - September 2005) and Pediatric Research (1987 - September 2005). Unpublished trials were sought by handsearching the conference proceedings of American Pediatric Society/Society for Pediatric Research (1990 - 2005) and European Society for Paediatric Research (1993 - 2005).

Selection criteria

Randomised or quasi-randomised controlled trials of newborn infants receiving sodium bicarbonate infusion during any resuscitation in the delivery room at birth.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. Study authors were contacted for additional information.

Main results

We found one randomised controlled trial that fulfilled the eligibility criteria (Lokesh 2004) that compared treating asphyxiated newborn infants (infants continuing to need positive pressure ventilation at 5 minutes after birth) with sodium bicarbonate infusion (N = 27) versus 5% dextrose (N = 28). They found no evidence of an effect on mortality prior to discharge [Relative risk 1.04 (95% confidence

interval 0.49 to 2.21)], abnormal neurological examination at discharge [Relative risk 0.86 (95% confidence interval 0.30 to 2.50)] or a composite outcome of death or abnormal neurological examination at discharge [Relative risk 0.97 (95% confidence interval 0.59 to 1.60)]. There was no statistically significant difference in the incidence of encephalopathy [Relative risk 1.30 (95% confidence interval 0.88 to 1.92)], intraventricular haemorrhage [Relative risk 1.04 (95% confidence interval 0.23 to 4.70)] and neonatal seizures [Relative risk 1.19 (95% confidence interval 0.50 to 2.82)]. No long term neurodevelopmental outcomes were assessed.

Authors' conclusions

There is insufficient evidence from randomised controlled trials to determine whether the infusion of sodium bicarbonate reduces mortality and morbidity in infants receiving resuscitation in the delivery room at birth.

PLAIN LANGUAGE SUMMARY

Sodium bicarbonate infusion during resuscitation of infants at birth

Intravenous infusion of sodium bicarbonate to newborn babies during resuscitation in the delivery room at birth. At birth some babies who do not start breathing spontaneously have an abnormal amount of acid in their blood. To treat this, an alkaline drug, sodium bicarbonate, has often been given intravenously. Although this has been common practice for over thirty years, there is no good evidence that this is beneficial and may cause harm. We found only one high quality study of 55 babies that compared sodium bicarbonate treatment with no treatment. The study did not show any benefit of the use of this drug immediately after birth, nor any adverse effects.

BACKGROUND

Approximately 5% to 10% of newborn infants require some active resuscitation at birth (Saugstad 1998). However, only a very small proportion will need chest compressions and drugs are rarely indicated (Perlman 1995). Intravenous sodium bicarbonate, a base, has been used to reverse acidosis during newborn resuscitation for many years, but controversy has surrounded its use.

The most recent international consensus guidelines for neonatal resuscitation state that "there is insufficient data to recommend routine use of sodium bicarbonate in resuscitation of the newly born. Its use is discouraged during brief cardiopulmonary resuscitation and if it is used during prolonged arrests unresponsive to other therapy, it should be given only after establishment of adequate ventilation and circulation" (Niermeyer 2000). However, a recent audit of neonatal resuscitation practice revealed a high rate (14%) of medication use in the delivery room (Mitchell 2002) and the Resuscitation Council (UK) recommends administration of sodium bicarbonate when there is no effective cardiac output, or virtually none, prior to a second dose of adrenaline. It is argued that reversing myocardial acidosis may help improve cardiac function (NLS 2001), particularly since adrenaline has been shown to be less effective during acidosis (Nakanishi 1987; Preziosi 1993) and cannot bind to its receptors at very low pH (Modest 1995).

When there is insufficient oxygen delivery to the fetus before delivery, peripheral vasoconstriction and redistribution of oxygen to vital organs occurs. Perfusion failure results in tissue hypoxia, depletion of high-energy phosphate stores and anaerobic metabolism leading to a mixed respiratory and metabolic acidosis. This acidaemia causes a right shift in the haemoglobin-oxygen dissociation curve, which furthers lowers blood oxygen content. Hypoxaemia and acidosis also contribute to a high pulmonary vascular resistance that results in an intrapulmonary right to left shunt. Eventually, increasing acidosis leads to cessation of gasping, poor myocardial contractility, bradycardia and finally to cardiac arrest.

Sodium bicarbonate and tris-hydroxymethyl-aminomethane (THAM) have both been used to correct metabolic acidosis in neonates. Under conditions of controlled normocapnia, sodium bicarbonate is a more potent alkalising agent than THAM when used in equimolar doses (Nudel 1993). THAM may cause hypoglycaemia, produce severe vasospasm, apnoea, induce arterial vasodilatation, reduce aortic diastolic pressure and markedly lower coronary artery perfusion (Kette 1991). THAM also delivers a greater osmolar load than sodium bicarbonate (Heird 1972). Sodium bicarbonate has, therefore, become the preferred alkalising agent in resuscitation. Bicarbonate functions as a physiologic buffer, but only in an open system in which carbon dioxide can be transported to the lungs and eliminated (Ostrea 1972), according to the Henderson-Hasselbach equation $H^+ + HCO_{3-}$ $H_20 + CO_2$. The excretion of CO_2 directs the reaction to the right, and thereby permits bicarbonate to play an important role in buffering the hydrogen ion.

Evidence emerged in the 1960's supporting the use of base in newborn resuscitation. Experiments on fetal lambs and monkeys

demonstrated that an infusion of glucose and sodium carbonate prolonged survival after asphyxia, facilitated recovery and possibly lessened the degree of cerebral injury (Dawes 1963). Rapid infusion of alkali in asphyxiated mature fetal monkeys prolonged gasping and reduced the time required to establish rhythmic breathing (Adamsons 1963).

However, there has been doubt concerning the benefit of using alkalizing agents during hypoxic lactic acidosis. In the absence of adequate ventilation, bicarbonate may induce paradoxical tissue and intracellular hypercarbic acidosis, especially since CO_2 moves more rapidly across cell membranes than bicarbonate (Ostrea 1972). A transient decrease in intramyocardial pH (Kette 1990), cardiac output and blood pressure (Graf 1985) and no improvement in the ability to resuscitate (Weil 1985) have all been observed after bicarbonate administration. It has been shown that the important correlate of successful resuscitation is improved coronary perfusion pressure and not pH (Kette 1990), and bicarbonate may even worsen myocardial perfusion (Kette 1991).

A recent review concluded that sodium bicarbonate treatment in newborn infants is more likely to lead to problems than to facilitate resuscitation (Wyckoff 2001). The hyperosmolar nature of sodium bicarbonate can result in fluid shifts that cause cells, including red blood cells, to lose water, thus increasing their intracellular ionic strength (Ostrea 1972). Proteins then become stronger acids and generate additional acid by releasing protons (Howell 1987). Increased plasma osmolality has also been associated with a significant decrease in coronary perfusion pressure (Kette 1991). Rapid injection of hypertonic bicarbonate may cause increases in intravascular volume and venous pressure with profound fluid shift effects on the brain, resulting in cerebral shrinkage and haemorrhage (Finberg 1977). Observational studies have linked hypertonic bicarbonate therapy with intraventricular haemorrhage in preterm infants (Synnes 2001), especially when given rapidly and in large quantities (Simmons 1974; Papile 1978a). Loss of cerebral autoregulation and decreased cerebral blood flow have been reported (Lou 1978). A recent Cochrane Review cautioned on the potential neurodevelopmental effects of rapid injections of bicarbonate (Kecskes 2001).

On the other hand, concerns have been raised about the long-term effect of metabolic acidosis during the newborn period. Cerebral vascular resistance is decreased in the first week of life in term infants who had metabolic acidosis at delivery (Morrison 1995). Metabolic acidosis in newborn preterm infants has been associated with periventricular leucomalacia (Low 1990) and an inverse relationship between the degree of acidosis at birth and cognitive abilities between four and seven years of age has been demonstrated in term and preterm infants (Stevens 1999).

Most of the evidence to establish the use of sodium bicarbonate in neonatal resuscitation has been derived from studies in either animals or adult humans and uncontrolled, descriptive, experimental investigations. The aim of this review is to determine whether there is any evidence from randomised controlled trials in the human neonatal population to recommend sodium bicarbonate infusion during resuscitation at birth.

OBJECTIVES

Primary objective :

To determine whether the infusion of sodium bicarbonate, compared to placebo or no treatment, reduces mortality in infants receiving resuscitation in the delivery room at birth.

Secondary objectives :

(a) To determine whether the infusion of sodium bicarbonate to infants receiving resuscitation at birth reduces morbidity, in particular short and long-term neurological disability

(b) To determine whether the infusion of sodium bicarbonate to infants receiving resuscitation at birth is more effective and safer than other alkalising agents

Subgroup analyses are planned to determine whether the effect of sodium bicarbonate on mortality and morbidity varies with:

(i) gestational age, i.e. term (greater than or equal to 37 weeks) versus preterm (less than 37 weeks)

(ii) condition at birth as measured by Apgar score at one minute, i.e. Apgar score 0 versus $\geq$ 1

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials.

Types of participants

Newborn infants (both preterm and term) who receive any resuscitation intervention in the delivery room at birth.

Types of interventions

Sodium bicarbonate infusion (at any dosage or rate) compared with control (placebo or no treatment).
Sodium bicarbonate infusion compared with other alkalising agents (e.g. THAM).
All studies which involve co-interventions, e.g. external cardiac compression, adrenaline, will be eligible.

Types of outcome measures

Primary outcomes:
1. Death - in delivery room
Secondary outcomes:
1. Death - before seven days, before 28 days, prior to discharge from hospital
2. Long term severe neurodevelopmental disability reported at any time during follow up. Defined as any of cerebral palsy, cognitive delay (score > 2 SD below mean for a recognised psychometric test e.g. Bayley scales), blindness and deafness
3. Intraventricular haemorrhage - any or severe (grades three and four) as defined by Papile (Papile 1978b)
4. Periventricular leucomalacia
5. Neonatal seizures - detection based either on clinical grounds, EEG or requirement for anti-epileptic medication
6. Signs consistent with hypoxic ischaemic encephalopathy grades I-III (Sarnat 1976)
7. Abnormal neurological examination at discharge
8. Necrotising enterocolitis - Bell's stage II and III (Bell 1978)

Search methods for identification of studies

The standard search strategy of the Neonatal Review Group as outlined in The Cochrane Library was used. See Review Group details for more information.
This included searches of
1. CENTRAL - Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 3, 2005)
2. Electronic journal reference databases
a. MEDLINE (1966 - present)
b. EMBASE (1980 - present)
c. CINAHL (1982 - present)
3. Oxford Database of Perinatal Trials
4. Abstracts and proceedings of conferences including
a. American Pediatric Society / Society for Pediatric Research (1990 - present)
b. European Society for Paediatric Research (1993 - present)
5. Pediatric Research (1987 - present)
6. Dissertations and relevant doctoral theses through Dissertation Abstracts on disc (1960 - present) provided by the Radcliffe Science Library, Oxford were identified and those fulfilling the selection criteria retrieved in full.
7. Communication with authors for more information if necessary on relevant published articles or abstracts and other prominent experts in the field for possible unpublished articles.
Whenever possible, investigators of eligible studies were contacted about additional studies suitable for inclusion.
8. Previous reviews, bibliographies of published trials and cross references.
The following search terms were used to search MEDLINE:
Infant, newborn (explode) [MeSH]
AND Resuscitation (explode) [MeSH]
OR Asphyxia neonatorum (explode) [MeSH]
OR Sodium bicarbonate (explode) [MeSH]
OR stillborn (tw)
OR stillbirth (tw)
OR birth (tw)
This search strategy was customised for the other electronic databases (CENTRAL, EMBASE, CINAHL). The title and abstract of each retrieved study was examined to assess eligibility. If there was uncertainty, the full paper was examined. No language restriction was applied.

Data collection and analysis

The standard method of the Cochrane Collaboration and its Neonatal Review Group was used to assess methodological quality of the trials.
At least two of the three review authors worked independently to search for and assess studies for their methodological quality for inclusion in the review. Studies were assessed for the following key criteria: allocation concealment (blinding of randomisation), blinding of intervention, completeness of follow-up and blinding of outcome measurement. These are reported as yes, no or can't tell. The full text of all studies of possible relevance was obtained. Data was extracted independently and additional information was requested from investigators of eligible studies where necessary. Any disagreement was resolved by discussion between the review authors.
Statistical analysis followed the standard procedures of the Cochrane Neonatal Review Group. Treatment effect was expressed using relative risk (RR), risk difference (RD) and number needed to treat (NNT), with 95% confidence intervals where appropriate. Heterogeneity between studies will be examined using the I^2 test. The main objective of this review is to compare sodium bicarbonate with no treatment or placebo. If trials were found that compare sodium bicarbonate with other alkalising agents, these were analysed as a separate comparison.
Subgroup analyses were performed where sufficient data was available for the following identified subcategories:
1. Term infants i.e. equal or greater than 37 weeks gestational age
2. Preterm infants i.e. less than 37 weeks gestational age
3. Infants with Apgar score 0 at one min
4. Infants with Apgar score $\geq$ 1 at one min

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

We identified four publications that describe the data from three randomised controlled trials for potential inclusion (Bland 1976; Corbet 1977; Lokesh 2004; Murki 2004).

Only one trial was eligible for inclusion (Lokesh 2004). Details are presented in the table: Characteristics of Included Studies.

This trial was reported in two separate publications (Lokesh 2004; Murki 2004) and we have confirmed with the authors that the study population in both papers was the same group of newborn infants. As each publication describes slightly different clinical outcome variables, both were used in this review. However, their data was only analysed once to ensure no duplication of results.

Lokesh 2004 randomly allocated 55 consecutively born asphyxiated newborn infants who continued to need positive pressure ventilation at five minutes after birth to receive either sodium bicarbonate (N = 27) or 5% dextrose (N = 28). The study group was given intravenous sodium bicarbonate solution 4 ml/kg (1.8 meq/kg) over 3 - 5 minutes (7.5% sodium bicarbonate (0.9 meq/ml) diluted with distilled water in a 1:1 ratio). The placebo group received intravenous 5% dextrose 4 ml/kg at a similar rate. Participating infants were followed up until discharge. The primary outcome variables were survival to discharge, abnormal neurological examination at discharge, and death or abnormal neurological examination at discharge (composite outcome). Other clinical secondary outcomes were occurrence of encephalopathy, neonatal seizures, multi-organ dysfunction and intraventricular haemorrhage.

Two trials were excluded (Bland 1976; Corbet 1977). Details are presented in the table: Characteristics of Excluded Trials.

1. Bland 1976 randomly allocated 51 hypoproteinaemic (umbilical cord serum protein $\leq$ 4.6 gm/100ml) preterm infants "at risk of developing acidaemia" to receive either an infusion of sodium bicarbonate over 5 to 10 minutes or an infusion of glucose or albumin within the first two hours after birth. Treatment was commenced only after admission to the neonatal unit rather than during resuscitation at birth. This trial was excluded due to the late enrolment of infants.

2. Corbet 1977 randomly allocated 62 newborn preterm infants within the first few hours after birth to receive either a "liberal" or "conservative" bicarbonate infusions, given with their standard maintenance intravascular infusions of 10% glucose. The age of enrolment was 3.6 + 0.4 hr in the liberal group and 4.1 $\pm$ 0.6 hr in the conservative group. This trial was excluded due to the late enrolment of infants into the study.

Risk of bias in included studies

Lokesh 2004 randomised consecutively born asphyxiated neonates requiring positive pressure ventilation at five minutes after birth to each comparison group using a computer generated sequence and achieved satisfactory allocation concealment. It was unclear whether there was blinding of the intervention during newborn resuscitation. The care providers and assessors were blinded to the intervention. Follow up was complete.

There was no disagreement regarding inclusion and exclusion of studies, quality assessment or data extraction.

Effects of interventions

Infusion of sodium bicarbonate versus placebo or no treatment

1. Death - in delivery room

No study reported this outcome.

2. Death - prior to discharge from hospital (table 01.01):

Lokesh 2004 did not find evidence of an effect on mortality prior to discharge: Relative risk 1.04 (95% confidence interval 0.49 to 2.21), risk difference 0.01(95% confidence interval -0.24 to 0.26).

3. Abnormal neurological examination at discharge (table 01.02):

Lokesh 2004 did not find a statistically significant difference in the incidence of abnormal neurological examination at discharge: Relative risk 0.86 (95% confidence interval 0.30 to 2.50), risk difference -0.03 (95% confidence interval -0.24 to 0.18).

4. Death or abnormal neurological examination at discharge (composite outcome) (table 01.03):

Lokesh 2004 did not find evidence of an effect on this composite outcome: Relative risk 0.97 (95% confidence interval 0.59 to 1.60), risk difference -0.02 (95% confidence interval -0.28 to 0.25).

5. Encephalopathy (table 01.04):

Lokesh 2004 did not find a statistically significant difference in the incidence of encephalopathy: Relative risk 1.30 (95% confidence interval 0.88 to 1.92), risk difference 0.17 (95% confidence interval -0.08 to 0.42).

6. Intraventricular haemorrhage (table 01.05):

Lokesh 2004 did not find a statistically significant difference in the incidence of intraventricular haemorrhage: Relative risk 1.04 (95% confidence interval 0.23 to 4.70), risk difference 0.00 (95% confidence interval -0.16 to 0.17).

7. Neonatal seizures (table 01.06)

Murki 2004 did not find a statistically significant difference in the incidence of neonatal seizures: Relative risk 1.19 (95% confidence interval 0.50 to 2.82), risk difference 0.05 (95% confidence interval -0.19 to 0.28).

8. Long term severe neurodevelopmental disability reported at any time during follow up

No study reported this outcome.

9. Periventricular leucomalacia

No study reported this outcome.

10. Necrotising enterocolitis

No study reported this outcome.

Infusion of sodium bicarbonate versus other alkalizing agents
There were no eligible trials.
Subgroup analyses

1. Gestational age i.e. term (greater than or equal to 37 weeks) versus preterm (less than 37 weeks)

Lokesh 2004 carried out a subgroup analysis of term and preterm babies separately and found no difference between the bicarbonate and control groups for survival to discharge, abnormal neurological examination at discharge or composite outcome among term and preterm babies.
2. Condition at birth as measured by Apgar score at 1 min
A planned subgroup analysis based on the condition of the infant at birth was not possible. The results of the included study were not presented stratified by Apgar score.

DISCUSSION

This review found only one randomised controlled trial which addressed the use of sodium bicarbonate in newborn resuscitation (Lokesh 2004). The available data did not show any evidence of any benefit or adverse effect of using a single infusion of sodium bicarbonate during the resuscitation of the newborn infant. All outcomes were statistically non-significant and were short-term (up to discharge). No studies were available to provide data on any long-term outcomes.

It is not known whether term and preterm infants respond differently to sodium bicarbonate during resuscitation. Lokesh 2004 carried out a subgroup analysis of term and preterm babies separately and found no difference between the bicarbonate and control groups for survival to discharge, abnormal neurological examination at discharge or composite outcome among term and preterm babies. One of the concerns raised about sodium bicarbonate is the risk of intraventricular haemorrhage in preterm infants (Kecskes 2001; Papile 1978a; Simmons 1974; Simmons 1974). The details relating to intraventricular haemorrhage from their subgroup analysis were unpublished so we were unable to determine whether the preterm infants in this trial were more at risk of intraventricular haemorrhage. Access to unpublished data would also have enabled us to carry out subgroup analyses on initial Apgar score.

Those who advocate the use of a rapid injection of sodium bicarbonate in newborn resuscitation (NLS 2001) argue that this is intended to 'kick start' the heart. The rationale for its use is to correct myocardial acidosis prior to a second dose of adrenaline. However, Murki 2004 showed that sodium bicarbonate did not have any beneficial effect on arterial acid-base status in the first 24 hours. The mean pH and base deficits of both treatment and control group were similar at 1, 6, 12 and 24 hours of life (Murki 2004). Neither of the two excluded randomised controlled trials (Bland 1976; Corbet 1977) support the correction of metabolic acidosis. Bland 1976 compared 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, and found no differences in mortality, intracranial haemorrhage or incidence of respiratory distress syndrome. There was a trend to increased mortality and incidence of intracranial haemorrhage in the groups treated with sodium bicarbonate (Bland 1976). Corbet 1977 compared slow correction of acidaemia with no correction in preterm infants and showed no benefit in terms of the rate of pH-correction, mortality or incidence of intraventricular haemorrhage.

Although sodium bicarbonate has been used in neonatal clinical practice for a long time, there remains a lack of evidence from randomised controlled trials in humans to support its use in newborn resuscitation. This review has been unable to determine whether sodium bicarbonate infusion in newborn resuscitation reduces mortality or morbidity or is associated with significant adverse effects.

AUTHORS' CONCLUSIONS

Implications for practice

Currently, there is insufficient data from randomised controlled trials to make recommendations for clinical practice. We found only one randomised controlled trial which neither supported nor refuted the use of sodium bicarbonate during the resuscitation of infants in the delivery room at birth.

Implications for research

If sodium bicarbonate continues to be used during the resuscitation of newborn infants, despite this lack of evidence, there is a need for high quality randomised controlled trials with a larger number of infants to clarify whether there is any benefit for this intervention without significant harm. Any trial should include long-term follow up of participants looking at severe neurodevelopmental disability such as cerebral palsy, cognitive delay, blindness and deafness. Any trial should also include and stratify term and preterm infants and report outcomes in both groups.

Given the lack of any evidence that an intravenous infusion of sodium bicarbonate to correct metabolic acidosis during newborn resuscitation (Lokesh 2004; Murki 2004) confers significant benefit, it may be prudent to concentrate on studying other aspects of newborn resuscitation such as prevention of hypothermia, airway manoeuvres, ventilation and circulatory support, before spending resources on further studies of sodium bicarbonate.

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REFERENCES

References to studies included in this review

Lokesh 2004 *{published data only}*

* Lokesh L, Kumar P, Murki S, Narang A. A randomized controlled trial of sodium bicarbonate in neonatal resuscitation - effect on immediate outcome. *Resuscitation* 2004;**60**:219–23.

Murki M, Kumar P, Lingappa L, Narang A. Effect of a single dose of sodium bicarbonate given during neonatal resuscitation at birth on the acid-base status on first day of life. *Journal of Perinatology* 2004; **24**:696–9.

References to studies excluded from this review

Bland 1976 *{published data only}*

Bland RD, Clarke TL, Harden LB. Rapid infusion of sodium bicarbonate and albumin into high-risk premature infants soon after birth: a controlled, prospective trial. *American Journal of Obstetrics and Gynaecology* 1976;**124**:263–7.

Corbet 1977 *{published data only}*

Corbet AJ, Adams JM, Kenny JD, Kennedy J, Rudolph AJ. Controlled trial of bicarbonate therapy in high-risk premature newborn infants. *Journal of Pediatrics* 1977;**91**:771–6.

Additional references

Adamsons 1963

Adamsons K Jr, Behrman R, Dawes GS, Dawkins MJ, James LS, Ross BB. The treatment of acidosis with alkali and glucose during asphyxia in foetal rhesus monkeys. *Journal of Physiology* 1963;**169**: 679–89.

Bell 1978

Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, Brotherton T. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Annals of Surgery* 1978;**187**: 1–7.

Dawes 1963

Dawes GS, Jacobson HN, Mott JC, Shelley HJ, Stafford A. The treatment of asphyxiated, mature foetal lambs and rhesus monkeys with intravenous glucose and sodium carbonate. *Journal of Physiology* 1963;**169**:167–84.

Finberg 1977

Finberg L. The relationship of intravenous infusions and intracranial hemorrhage - a commentary. *Journal of Pediatrics* 1977;**91**:777–8.

Graf 1985

Graf H, Leach W, Arieff AI. Evidence of detrimental effect of bicarbonate therapy in hypoxic lactic acidosis. *Science* 1985;**227**:754–6.

Heird 1972

Heird WC, Dell RB, Price T, Winters RW. Osmotic effects of infusion of THAM. *Pediatric Research* 1972;**6**:495–503.

Howell 1987

Howell JH. Sodium bicarbonate in the perinatal setting --revisited. *Clinics of Perinatology* 1987;**14**:807–16.

Kecskes 2001

Kecskes ZB, Davies MW. Rapid correction of early metabolic acidaemia in comparison with placebo, no intervention or slow correction in LBW infants. *The Cochrane Database of Systematic Reviews* 2004, Issue 1.[Art. No.: CD002976. DOI: 10.1002/14651858.CD002976]

Kette 1990

Kette F, Weil MH, von Planta M, Gazmuri RJ, Rackow EC. Buffer agents do not reverse intramyocardial acidosis during cardiac resuscitation. *Circulation* 1990;**81**:1660–6.

Kette 1991

Kette F, Weil H, Gazmuri RJ. Buffer solutions may compromise cardiac resuscitation by reducing coronary perfusion pressure. *JAMA* 1991;**266**:2121–6.

Lou 1978

Lou HC, Lassen NA, Friis-Hansen B. Decreased cerebral blood flow after administration of sodium bicarbonate in the distressed newborn infant. *Acta Neurologica Scandinavica* 1978;**57**:239–47.

Low 1990

Low JA, Froese AF, Galbraith RS, Sauerbrei EE, McKinven JP, Karchmar EJ. The association of fetal and newborn metabolic acidosis with severe periventricular leukomalacia in the preterm newborn. *American Journal of Obstetrics and Gynecology* 1990;**162**:977–81.

Mitchell 2002

Mitchell A, Niday P, Boulton J, Chance G, Dulberg C. A prospective clinical audit of neonatal resuscitation practices in Canada. *Advances in Neonatal Care* 2002;**2**:316–26.

Modest 1995

Modest VE, Butterworth JF 4th. Effect of pH and lidocaine on beta-adrenergic receptor binding: Interaction during resuscitation?. *Chest* 1995;**108**:1373–9.

Morrison 1995

Morrison FK, Patel NB, Howie PW, Mires GJ, Herd RM. Neonatal cerebral arterial flow velocity waveforms in term infants with or without metabolic acidosis at delivery. *Early Human Development* 1995;**42**:155–68.

Murki 2004

Murki M, Kumar P, Lingappa L, Narang A. Effect of a single dose of sodium bicarbonate given during neonatal resuscitation at birth on the acid-base status on first day of life. *Journal of Perinatology* 2004; **24**:696–9.

Nakanishi 1987

Nakanishi T, Okuda H, Kamata K, Seguchi M, Nakazawa M, Takao A. Influence of acidosis on inotropic effect of catecholamines in newborn rabbit hearts. *American Journal of Physiology* 1987;**253**:H1441–8.

Niermeyer 2000

Niermeyer S, Kattwinkel J, Van Reempts P, Nadkami V, Phillips B, Zideman D, et al.International Guidelines for Neonatal Resuscitation: An excerpt from the Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: International Consensus on Science. Contributors and Reviewers for the Neonatal Resuscitation Guidelines. *Pediatrics* 2000;**106**:E29.

NLS 2001

Resuscitation Council (UK). Resuscitation at birth. Newborn Life Support Manual 2001.

Nudel 1993

Nudel DB, Camara A, Levine M. Comparative effects of bicarbonate, tris-(hydroxymethyl)aminomethane and dichloroacetate in newborn swine with normoxic lactic acidosis. *Developmental Pharmacology and Therapeutics* 1993;**20**:20–5.

Ostrea 1972

Ostrea EM Jr, Odell GB. The influence of bicarbonate administration on blood pH in a "closed system": clinical implications. *Journal of Pediatrics* 1972;**80**:671–80.

Papile 1978a

Papile LA, Burstein J, Burstein R, Koffler H, Koops B. Relationship of intravenous sodium bicarbonate infusions and cerebral intraventricular hemorrhage. *Journal of Pediatrics* 1978;**93**:834–6.

Papile 1978b

Papile LA, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *Journal of Pediatrics* 1978;**92**: 529–34.

Perlman 1995

Perlman JM, Risser R. Cardiopulmonary resuscitation in the delivery room. Associated clinical events. *Archives of Pediatrics & Adolescent Medicine* 1995;**149**:20–5.

Preziosi 1993

Preziosi MP, Roig JC, Hargrove N, Burchfield DJ. Metabolic acidemia with hypoxia attenuates the hemodynamic responses to epinephrine during resuscitation in lambs. *Critical Care Medicine* 1993;**21**:1901–7.

Sarnat 1976

Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. *Archives of Neurology* 1976;**33**:696–705.

Saugstad 1998

Saugstad OD. Practical aspects of resuscitating asphyxiated newborn infants. *European Journal of Pediatrics* 1998;**157**:S11–S15.

Simmons 1974

Simmons MA, Adcock EW 3rd, Bard H, Battaglia FC. Hypernatremia and intracranial hemorrhage in neonates. *The New England Journal of Medicine* 1974;**291**:6–10.

Stevens 1999

Stevens CP, Raz S, Sander CJ. Peripartum hypoxic risk and cognitive outcome: a study of term and preterm birth children at early school age. *Neuropsychology* 1999;**13**:598–608.

Synnes 2001

Synnes AR, Chien LY, Peliowski A, Baboolal R, Lee SK, Canadian NICU Network. Variations in intraventricular hemorrhage incidence rates among Canadian neonatal intensive care units. *Journal of Pediatrics* 2001;**138**:525–31.

Weil 1985

Weil MH, Trevino RP, Rackow EC. Sodium bicarbonate during CPR. Does it help or hinder?. *Chest* 1985;**88**:487.

Wyckoff 2001

Wyckoff MH, Perlman J, Niermeyer S. Medications during resuscitation - what is the evidence?. *Seminars in Neonatology* 2001;**6**: 251–9.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Lokesh 2004

Methods	Randomised controlled trial. Blinding of randomisation: yes Blinding of intervention: can't tell Complete follow-up: yes Blinding of outcome measurement: yes
Participants	Consecutively born asphyxiated neonates continuing to need positive pressure ventilation at 5 minutes after birth. Babies with major congenital malformations excluded.
Interventions	1. Sodium bicarbonate 4 ml/kg (1.8 meq/kg) intravenous infusion over 3-5 min (N=27) versus 2. 5% dextrose 4 ml/kg intravenous infusion over 3-5 min (N=28)
Outcomes	Lokesh 2004 Primary: Survival, abnormal neurological examination at discharge, death or abnormal neurological examination at discharge (composite outcome). Secondary: Encephalopathy, multi-organ dysfunction, intraventricular haemorrhage, cerebral oedema, arterial pH at 6 hours. Murki 2004 Primary: Acid-base status at 1, 6, 12 and 24 hours of life Secondary: Encephalopathy, neonatal seizures, cerebral oedema
Notes	Lokesh 2004 and Murki 2004 publications report the same randomised controlled trial.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Bland 1976	Late entry to study - enrolment after admission to NICU and not during resuscitation in the delivery room.
Corbet 1977	Late entry to study - enrolment after admission to NICU and not during resuscitation in the delivery room. Average age > 3 hours.

DATA AND ANALYSES

Comparison 1. Sodium bicarbonate versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death prior to discharge	1	55	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.49, 2.21]
2 Abnormal neurological examination at discharge	1	55	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.30, 2.50]
3 Death or abnormal neurological examination at discharge	1	55	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.59, 1.60]
4 Encephalopathy	1	55	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.88, 1.92]
5 Intraventricular haemorrhage	1	55	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.23, 4.70]
6 Neonatal seizures	1	55	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.50, 2.82]

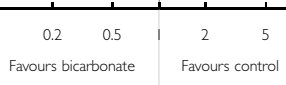
Analysis 1.1. Comparison 1 Sodium bicarbonate versus placebo or no treatment, Outcome 1 Death prior to discharge.

Review: Sodium bicarbonate infusion during resuscitation of infants at birth

Comparison: 1 Sodium bicarbonate versus placebo or no treatment

Outcome: 1 Death prior to discharge

Study or subgroup	Bicarbonate n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Lokesh 2004	9/27	9/28		100.0 %	1.04 [0.49, 2.21]
Total (95% CI)	**27**	**28**		**100.0 %**	**1.04 [0.49, 2.21]**
Total events: 9 (Bicarbonate), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.09 (P = 0.93)					



Analysis 1.2. Comparison 1 Sodium bicarbonate versus placebo or no treatment, Outcome 2 Abnormal neurological examination at discharge.

Review: Sodium bicarbonate infusion during resuscitation of infants at birth

Comparison: 1 Sodium bicarbonate versus placebo or no treatment

Outcome: 2 Abnormal neurological examination at discharge

Study or subgroup	Bicarbonate n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Lokesh 2004	5/27	6/28		100.0 %	0.86 [0.30, 2.50]
Total (95% CI)	**27**	**28**		**100.0 %**	**0.86 [0.30, 2.50]**
Total events: 5 (Bicarbonate), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.27 (P = 0.79)					

Analysis 1.3. Comparison 1 Sodium bicarbonate versus placebo or no treatment, Outcome 3 Death or abnormal neurological examination at discharge.

Review: Sodium bicarbonate infusion during resuscitation of infants at birth

Comparison: 1 Sodium bicarbonate versus placebo or no treatment

Outcome: 3 Death or abnormal neurological examination at discharge

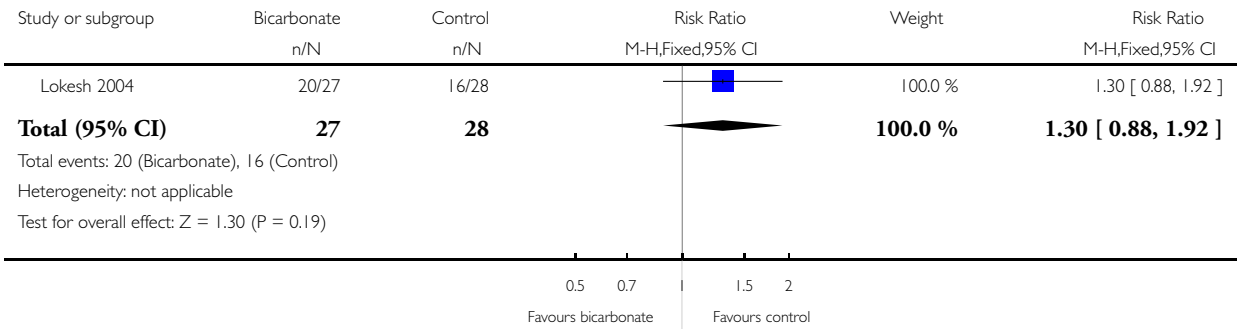
Study or subgroup	Bicarbonate n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Lokesh 2004	14/27	15/28		100.0 %	0.97 [0.59, 1.60]
Total (95% CI)	**27**	**28**		**100.0 %**	**0.97 [0.59, 1.60]**
Total events: 14 (Bicarbonate), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.13 (P = 0.90)					

Analysis 1.4. Comparison 1 Sodium bicarbonate versus placebo or no treatment, Outcome 4 Encephalopathy.

Review: Sodium bicarbonate infusion during resuscitation of infants at birth

Comparison: 1 Sodium bicarbonate versus placebo or no treatment

Outcome: 4 Encephalopathy

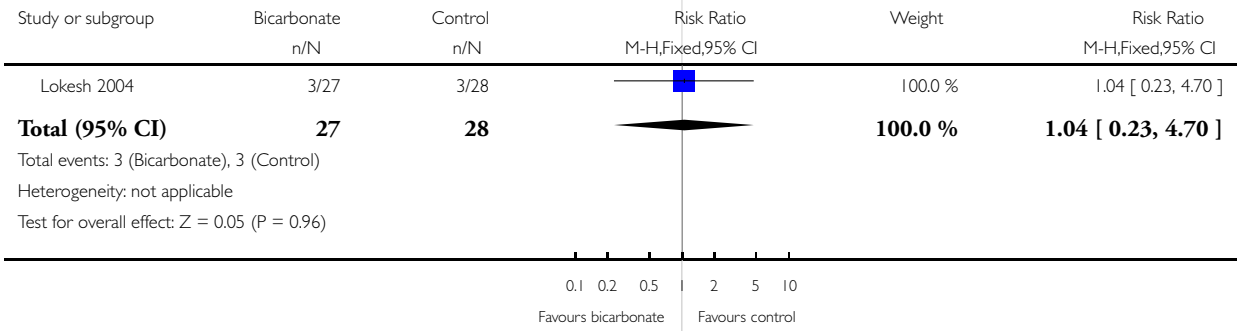


Analysis 1.5. Comparison 1 Sodium bicarbonate versus placebo or no treatment, Outcome 5 Intraventricular haemorrhage.

Review: Sodium bicarbonate infusion during resuscitation of infants at birth

Comparison: 1 Sodium bicarbonate versus placebo or no treatment

Outcome: 5 Intraventricular haemorrhage

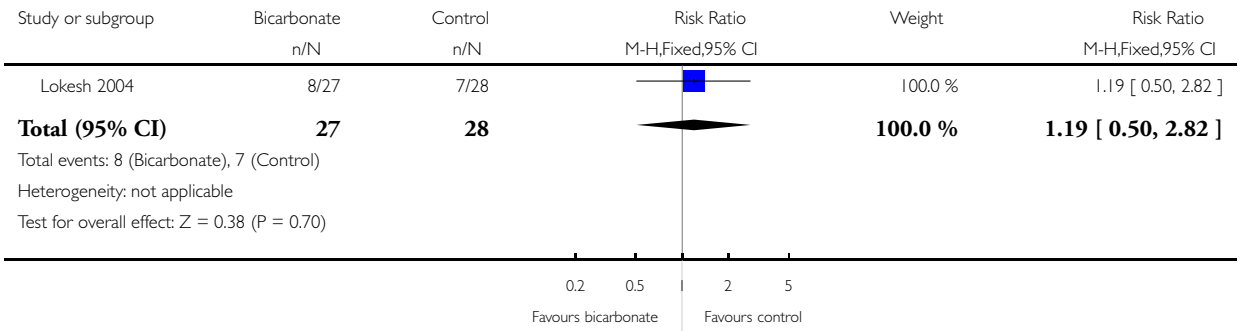


Analysis 1.6. Comparison 1 Sodium bicarbonate versus placebo or no treatment, Outcome 6 Neonatal seizures.

Review: Sodium bicarbonate infusion during resuscitation of infants at birth

Comparison: 1 Sodium bicarbonate versus placebo or no treatment

Outcome: 6 Neonatal seizures



WHAT'S NEW

Last assessed as up-to-date: 29 September 2005.

30 October 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 1, 2006

30 September 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Beveridge CJE (CJEB) wrote the protocol, carried out the searches, analysed the data and wrote the final review.

Wilkinson AR (ARW) edited the protocol, analysed the data and edited the final review.

Amit Gupta (AG) assisted with the literature search.

DECLARATIONS OF INTEREST

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Asphyxia Neonatorum [*drug therapy]; Glucose [administration & dosage]; Infant, Newborn; Infusions, Intravenous; Randomized Controlled Trials as Topic; Resuscitation [*methods]; Sodium Bicarbonate [*administration & dosage]

MeSH check words

Humans