**WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**

**Worksheet author(s)**

| Date Submitted for review: 10/15/2008 NRP-021A |

**Clinical question.**

In neonates requiring resuscitation and not responding to CPR (P) does the administration of sodium bicarbonate (I) versus no bicarbonate (C) improve outcome (O)

**Is this question addressing an intervention/therapy, prognosis or diagnosis?** Therapy

**State if this is a proposed new topic or revision of existing worksheet:** Second update

**Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

**Search strategy (including electronic databases searched).**

Ovid, Medline from 2004-2008 Mesh terms Neonates and/or resuscitation and/or CPR and sodium bicarbonate and/or asphyxia and/or infant and/or delivery room. Relevant hits: infant and/or newborn and bicarbonate (17 hits), sodium bicarbonate and delivery room + resuscitation (165 hits), sodium bicarbonate + delivery room (4 hits) - Two new studies retrieved

Embase from 2004 to 2008 Same terms and combinations – same two studies retrieved

Cochrane library – one review found CD004864 2006

ECC endnote library – no new study found

References from the most recent review articles

- **State inclusion and exclusion criteria**
  - Any neonatal study related to sodium bicarbonate administration during acute cardiac arrest, neonatal animal studies. Non English language articles were searched

- **Number of articles/sources meeting criteria for further review:**
  - Two new articles were found that met criteria for review and inclusion in the worksheet. Thus there are now 23 articles contained in the worksheet
## Summary of evidence

### Evidence Supporting Clinical Question

In neonates requiring resuscitation and not responding to CPR(P) does the administration of sodium bicarbonate (I) versus no bicarbonate (C) improve outcome(O)

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### Level of evidence

- **A** = Return of spontaneous circulation
- **C** = Survival to hospital discharge
- **E** = Other endpoint
- **B** = Survival of event
- **D** = Intact neurological survival
- **Italics** = Animal studies

Blue = Adult studies
## Evidence Neutral to Clinical question

In neonates requiring resuscitation and not responding to CPR(P) does the administration of sodium bicarbonate (I) versus no bicarbonate (C) improve outcome(O)

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REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

The role of sodium bicarbonate during resuscitation remains controversial. There are concerns that in the absence of adequate ventilation, sodium bicarbonate administration can exacerbate intracellular hypercarbia worsening intracellular acidosis. Moreover as a secondary consequence either directly or indirectly, there may be impaired myocardial function. In the premature infant infusion of sodium bicarbonate may result in the development of intraventricular hemorrhage (Simmons, 1974)(LOE 5). There is a small randomized neonatal study in “asphyxiated “ term infants (low five minute Apgar score and requiring bag/mask positive pressure ventilation that failed to demonstrate any beneficial effect of sodium bicarbonate administration on neurologic outcome or survival (Lokesh, 2004,Beveridge, 2006)(LOE 1). Thus there was no effect on mortality prior to discharge [Relative risk (RR) 1.04 (95% confidence interval (CI) 0.49 to 2.21)], abnormal neurological examination at discharge [RR 0.86 (95% CI 0.30 to 2.50)] or a composite outcome of death or abnormal neurological examination at discharge [RR 0.97 (95% confidence interval 0.59 to 1.60)], incidence of encephalopathy [RR 1.30 (95% CI 0.88 to 1.92)], IVH [RR 1.04 (95% CI 0.23 to 4.70)] and neonatal seizures [RR 1.19 (95% CI 0.50 to 2.82)] noted. A recent studies failed to demonstrate any benefit from sodium bicarbonate administration on acid base status in the 24 hours following infusion (Murki (2004)(LOE 1). There are no neonatal animal studies that have addressed the specific role of bicarbonate in achieving recovery of spontaneous circulation or survival following CPR. A tangential neonatal animal study has noted attenuated hemodynamic responses to resuscitation with epinephrine and oxygen when concomitant acidosis was present (Preziosi, 1993)(LOE 5). However this model used a pure metabolic acidosis that is distinct from the mixed acidosis noted in the delivery room. In addition, acidosis was produced by the infusion of exogenous lactate, which may not adequately simulate acidosis derived from intracellular acid production as a result of cellular hypoxia.

Additional neonatal studies suggest that bicarbonate administration increases arterial pH, brain intracellular pH and PaCO2 without producing concomitant paradoxical brain intracellular acidosis provided adequate cardiac output is maintained (Sessler, 1987 Laptok, 1985)(LOE 5). However one neonatal human study reported significant reduction in cerebral blood flow (up to 50%) following bicarbonate infusion (Lou, 1978)(LOE 5). An evidence-based review of adult human and animal studies indicates that no human study has demonstrated a beneficial impact on survival and that several adult human studies (level of evidence 3 and 4) demonstrated deleterious effects on physiologic endpoints from the administration of bicarbonate during CPR (Levy, 1998). While several animal studies demonstrated impaired function in response to bicarbonate administration during CPR (Guerci, 1986, Wiklund, 1990. {Kette, 1991, Frederik, 1991, Rubertsson, 1993, Neumar, 1995}(LOE 5) others have demonstrated survival benefit from the administration of bicarbonate during CPR (Bar Joseph 1998, Bleske, 1992 Leong, 2001Vukmir, 1995)(LOE 5). In summarizing the clinical and animal observations, given the known and potential side effects of sodium bicarbonate infusions including depression of myocardial function from the osmolar load, paradoxical intracellular acidosis, reduction in cerebral blood flow and the risk for intraventricular hemorrhage, the use of sodium bicarbonate infusion should be discouraged during brief CPR, but sodium bicarbonate may be of some benefit in an infant with prolonged CPR unresponsive to other therapy including adequate ventilation.

Conclusion

DISCLAIMER: Potential possible wording for a Consensus on Science Statement. Final wording will differ due to other input and discussion.

CONSENSUS ON SCIENCE:

Evidence from two randomized clinical studies indicate no benefit from the administration of sodium bicarbonate to asphyxiated infants requiring resuscitation with regard to neurologic outcome, survival or acid base status (LOE 1 Lokesh 2004, 2004;219, Murki 200, 296)
One neonatal human study reported a significant reduction in cerebral blood flow (up to 50%) following bicarbonate infusion (LOE 5, Lou, 1978, 239)
TREATMENT RECOMMENDATION:

Acknowledgements:

Citation List

[Beveridge, 2006 #22] Beveridge, C. J. Wilkinson, A. R. Sodium bicarbonate infusion during resuscitation of infants at birth Cochrane Database of Systematic Reviews 2006 CD004864


Neonatal Clinical Studies

Beveridge, C. J. Wilkinson, A. R. Sodium bicarbonate infusion during resuscitation of infants at birth Cochrane Database of Systematic Reviews 2006 CD004864

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.


Results: One randomised controlled trial that fulfilled the eligibility criteria was found (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.

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.

Comment This is a Cochrane review of the Lokesh study (see below) the only randomized study evaluating the role of sodium bicarbonate infusion during resuscitation.

Level of Evidence 1-Quality Fair-Neutral


Abstract
Very little evidence is available that supports or disproves the use of medications in neonatal resuscitation. In this randomized controlled trial, we evaluated the effect of sodium bicarbonate given during neonatal resuscitation, on survival and neurological outcome at discharge.

SUBJECTS AND METHODS: Consecutively born asphyxiated neonates continuing to need positive pressure ventilation at 5 min of life received either sodium bicarbonate or 5% dextrose. The study group was given intravenous sodium bicarbonate solution 4 ml/kg (1.8 meq/kg) over 3-5 min. This solution was prepared by diluting 7.5% sodium bicarbonate (0.9 meq/ml) with distilled water in a 1:1 ratio. The placebo group received 4 ml/kg of undiluted 5% dextrose at a similar rate. The surviving neonates were evaluated for their neurological status at discharge. Primary outcome variable: Death or abnormal neurological examination at discharge. Secondary outcome variables: Encephalopathy, multi-organ dysfunction, intraventricular haemorrhage (IVH) and arterial pH at 6h. RESULTS: Twenty-seven babies were randomized to receive sodium bicarbonate (bicarb group) and 28 to receive 5% dextrose. Eighteen of the 27 (66.7%) babies in the bicarb group and 19 of the 28 babies (68%) in the dextrose group survived to discharge (P = 0.84). Twenty-eight percent of the survivors in the bicarb group and 32% of the survivors in the dextrose group were neurologically normal at discharge (P = 0.10). The composite primary outcome of death or abnormal neurological examination at discharge was similar in both groups (52% versus 54%, P = 0.88). The incidence of encephalopathy (74% versus 63%), cerebral oedema (52% versus 30%), need for inotropic support (44% versus 29%), intraventricular haemorrhage (IVH) and the mean arterial pH at 6 hrs were similar between the two groups. CONCLUSION: Administration of sodium bicarbonate during neonatal resuscitation did not help to improve survival or immediate neurological outcome.

Comment: Small randomized study that shows no benefit to the administration of sodium bicarbonate during resuscitation of the largely premature infant.

Level of Evidence: 1 - Quality Fair - Neutral


Contents

Methods: In the course of studies on cerebral blood flow in newborn infants the effect of sodium bicarbonate infusion on cerebral blood flow was noted. Cerebral blood flow was measured utilizing the 133Xe clearance technique before and after the treatment with 1 to 8 meq of sodium bicarbonate in seven distressed newborn infants. Results: In six of the seven cases a decrease in cerebral blood flow was noted, which in most cases range of reduction was 14 to 22 ml/100 g/min, which is about half the value prior to the bicarbonate infusion. In one case an extreme reduction occurred: cerebral blood flow was reduced to 3 ml/100 g/min, well below the level compatible with tissue survival.

Comments: The reduction in CBF may be secondary to bicarbonate induced cerebral vasoconstriction. The clinical implications of these observations are unclear.

Level of Evidence: 5 - Quality Fair - Opposing


Objective: To study the effect of a single dose of sodium bicarbonate given during neonatal resuscitation at birth on the acid-base status on the first day of life.

Methods: Tertiary care Level III NICU. A total of 55 consecutively born asphyxiated neonates continuing to receive positive pressure ventilation at 5 minutes of life were randomized to receive either 4 ml/kg (1.8 meq/kg) of sodium bicarbonate or 5% dextrose.

Results: The mean pH, base deficit and PaCO(2) were similar between the Base group and the Control group for the first 24 hours of life. The number of babies with persistent metabolic acidosis at 1, 6, 12 and 24 hours were comparable between the two groups.

Conclusion: Sodium bicarbonate given during neonatal resuscitation did not change the acid-base status in the first 24 hours of life.

Comment: No effect of sodium bicarbonate infusion

Level of Evidence: 1 - Quality Fair - Neutral


Methods: Retrospective chart review. The charts of infants admitted over 4 years to a neonatal intensive care unit were reviewed. The diagnosis of intracranial hemorrhage was made at autopsy in all but one case. Intracranial hemorrhage was associated with hypernatremia or excessive sodium administration in 25(81%) of the 32 cases. Following restrictive use of sodium bicarbonate, the incidence of hypernatremia decreased from 8.8 to 0.6% and the frequency of IVH declined from 13.4% to 2.6%.

Comments: The retrospective nature of the study in addition to establishing a diagnosis at autopsy precludes any definitive conclusions to be inferred from this data other than the association between two events.

Level of Evidence: 5 - Quality Fair - Opposing

Neonatal Animal Studies

Metabolic acidosis in the neonate is often secondary to hypoxemia and cardiopulmonary disturbances. Sodium bicarbonate, an agent used to treat metabolic acidemia in newborns, is often administered during hypoxemia. In the absence of acid-base alterations, during hypoxemia a reciprocal relationship exists between arterial O2 content (CaO2) and brain blood flow (BBF). However, when hypoxemia is compounded by acidemia it is unclear whether the increase in arterial pH achieved by infusions of sodium bicarbonate alters BBF.

Methods  BBF (microsphere technique), arterial blood gases, and CaO2 were measured in 14 ventilated piglets. Variables were assessed during a control period, a period of hypoxemia (50 min) associated with metabolic acidemia (hypoxemia + acidemia), and after infusions of either saline (n = 6) or NaHCO3 (n = 8, 2 mEq/kg) during continued hypoxemia. Results  Arterial pH was similar in both groups at control, and hypoxemia + acidemia resulted in comparable reductions of pH in both saline- and NaHCO3-treated piglets (7.21 +/- 0.02 versus 7.21 +/- 0.03, respectively). NaHCO3 infusions produced a significant rise in pH, 7.30 +/- 0.03 versus 7.15 +/- 0.03, p less than 0.05. In each group CaO2 paralleled changes in pH but did not differ between groups. In all animals BBF increased more than 2-fold during hypoxemia + acidemia and was unaltered by infusions of either saline or NaHCO3. Brain O2 delivery decreased in both groups during hypoxemia + acidemia and was unchanged by infusions of saline or NaHCO3. Conclusion  During hypoxemia + acidemia the change in arterial pH induced by NaHCO3 (2 mEq/kg) does not alter BBF or brain O2 delivery.

Comment  - Correction of metabolic acidosis does not appear to alter brain blood flow or oxygen delivery

Level of Evidence 5-Quality Good - Supportive


OBJECTIVE: To examine the effects of metabolic acidemia and hypoxia on the hemodynamic responses to epinephrine in an intact neonatal animal model.

Methods  Multi-experiment, randomized, controlled trial. Sixteen lambs, ranging in age from 2 to 14 days were chronically catheterized; the ductus arteriosus was ligated; and a pulmonary arterial flow probe was inserted to measure cardiac output, blood pressure (BP), and heart rate. In the first protocol, hemodynamic responses to epinephrine during pure metabolic acidemia or metabolic alkalosis were studied in eight lambs. Each lamb was studied on four different days at a different arterial pH: 6.9, 7.1, 7.4, and 7.6. Ventilation was controlled to maintain PCO2 at 35 to 45 torr (4.66 to 5.99 kPa). Acidemia was induced by the infusion of lactic acid and alkalosis by the infusion of sodium bicarbonate. When the appropriate arterial pH was achieved, 10 micrograms/kg of epinephrine was administered intravenously. In a second protocol, hemodynamic responses to epinephrine during metabolic acidemia or alkalosis plus hypoxia were studied in eight lambs. When the appropriate arterial pH was achieved, hypoxia was induced until cardiac output decreased to 40% of baseline. Epinephrine bolus was given, and after 90 secs, lambs were resuscitated with O2.

RESULTS: Epinephrine administered during uncompromised hemodynamics led to hypertension, bradycardia, and decreased cardiac output that were unaffected by arterial pH values between 6.9 and 7.6. Acidemia with hypoxia compromised hemodynamics with decreases in heart rate and cardiac output. Epinephrine administered during this compromised condition did not improve cardiac output, heart rate, or BP before resuscitation with oxygen at any arterial pH studied. Resuscitation with epinephrine and oxygen during hemodynamically compromised states led to increases in heart rate, BP, and cardiac output with significant attenuation of these hemodynamic responses during metabolic acidemia at pH values of 6.9 and 7.1.

CONCLUSIONS: During the physiologic conditions associated with neonatal resuscitation, that is, hypoxia with a compromised hemodynamic state, metabolic acidemia significantly attenuates the hemodynamic responses to resuscitation with epinephrine and oxygen. Correction of metabolic acidosis may be warranted in newborn resuscitation.

Comment  - Positive effect of correcting acidosis demonstrated on cardiovascular status. Note the PCO2 was maintained 35 to 45mmHg Again, I think it is interesting that no adverse effect of the exogenous acid administration was seen until they also made the lamb hypoxic compromising cardiac contractility. I really think this model is flawed with exogenous acid administration.

Level of Evidence 5-Quality Fair - Supportive


Objective  To determine whether administration of a neutralizing dose of bicarbonate in rabbits with lactic acidosis caused a paradoxical brain intracellular acidosis as measured by 31P spectroscopy. Methods Ten- to 16-day-old rabbits were anesthetized with 0.75% halothane/oxygen and their lungs mechanically ventilated. Metabolic acidosis was induced by decreasing PaO2 to 25 to 35 mm Hg for 1 to 2 hours until the base deficit was 10 to 15 mEq/L. Cerebral ischemia was prevented by maintaining arterial blood pressure at +/- 20% of control value with a venous infusion of epinephrine. Hypoxia was then terminated by administration of 100% oxygen, which was continued for the remainder of the study. After 15 minutes 100% oxygen, 5 mEq/kg 4.2% bicarbonate was administered to five animals; 5 minutes later the same dose was repeated. Control rabbits were given equal volumes of saline solution.

Results In all animals, arterial pH decreased from 7.43 +/- 0.06 to 7.25 +/- 0.08 (SE) during hypoxia, and brain intracellular pH from 7.22 +/- 0.06 to 7.09 +/- 0.09 (SE). Both pH values remained low during reoxygenation. Bicarbonate administration normalized arterial pH (7.41 +/- 0.03), whereas treatment with saline solution did not (7.23 +/- 0.01, P less than 0.05). PaCO2 rapidly increased by 10 mm Hg in the bicarbonate group, and remained elevated; it was unaffected by saline solution administration. Brain intracellular pH in the bicarbonate group increased by 0.12 U over 40 minutes, but intracellular pH in the saline solution group decreased 0.05 pH U (P less than 0.05) over the same period.

Comments Sodium bicarbonate infusion increased control pH, PCO2 as well as increasing brain intracellular pH. The “so called “paradoxical intracellular acidosis did not occur, however the bicarbonate was infused in the presence of adequate perfusion and ventilation.

Level of Evidence 5-Quality Good - Supportive
Wheeler, A. S. Sadri, S. Gutsche, B. B. et al. Intracranial hemorrhage following intravenous administration of sodium bicarbonate or saline solution in the newborn lamb asphyxiated in utero Anesthesiology 1979;51: 517-521

Background The effects of intravenously administered sodium bicarbonate was studied in near-term neonatal lambs asphyxiated in utero induced by maternal hypotension.

Methods Following tracheal intubation and manual ventilation with 100 per cent oxygen, the extracellular base deficits of ten neonates were corrected with sodium bicarbonate, 4.2 per cent, in 5 per cent dextrose (964 mOsm/l). Nine neonates alternatively received an isovolumic infusion of physiologic saline solution, 0.5 per cent, in 2.5 per cent dextrose (314 mOsm/l).

Results Following sodium bicarbonate infusion (mean dose 6.7 mEq/kg), serum sodium and osmolality immediately increased to 160 mEq/l and 335 mOsm/l, respectively. However, sodium values were similar in the two groups by 15 min after infusion. Although significant differences in PA(O2) values were not found between groups after infusion, sodium bicarbonate therapy was associated with a significantly higher PA(G2) value (175 +/- 60 torr) than was treatment with saline solution (51 +/- 8 torr) in neonates with pH(a)<7.00 before resuscitation. Significant disparities in pH(a) and base excess values occurred between bicarbonate- and saline-treated groups after infusion; two saline-treated lambs died, while all bicarbonate treated lambs survived the study period. Intracranial subarchnoid hemorrhage occurred in three bicarbonate- and in two saline-treated lambs and was apparently related to severe asphyxia and not to the toxicity of the solutions.

Conclusion Treatment of neonatal metabolic acidosis with appropriate doses of sodium bicarbonate is not associated with intracranial hemorrhage or sustained hypernatremia in the term neonatal lamb.

Comments Neonatal animal study that does not demonstrate a relationship to IVH. However the sheep model is distinctly different from the premature infant with a germinal matrix.

Level of Evidence 5-Quality Good - Neutral

Adult Clinical Studies


Contents Both adult and animal data

Methods Adult patient (n=6) received sodium bicarbonate infusion infusion and the blood was sampled.

Results: The administration of sodium bicarbonate was associated with an increase in pH from 7.38 ± 0.05 to 7.48±0.06, an increase in PaCO2 from 27±2.7 to 49±10mmHg and an increase in serum osmolality from 309 mOsm/kg to 349 mOsm/kg (all p <0.01) within two minutes. In control animals the pH decreased from 7.47±0.02 to 7.22±0.02 and the PCO2 decreased from 32±3.9 to 22±6mmHg

Methods 16 mongrel dogs subjected to VF and chest compressions initiated within three minutes were resuscitated with sodium bicarbonate 1mg/kg (n=9) and without (n=7) administered over 15 minutes.

Results. Sodium bicarbonate infusion was associated with an increase in pH from 7.23 ± 0.07 to 7.48±0.07, an increase in PaCO2 from 24±1.8 to 38±2.9mmHg and an increase in serum osmolality from 308 mOsm/kg to 343 mOsm/kg

Comments These studies demonstrate that (1) in the absence of preexisting acidosis, severe acidosis can be prevented by adequate ventilation alone; (2) sodium bicarbonate administration results in a significant rise in arterial PCO2, which parallels the rise in pH despite adequate ventilation; (3) during prolonged cardiac resuscitation, there is a rise in arterial osmolality that is accentuated by sodium bicarbonate. Furthermore these studies suggest that sodium bicarbonate should not be used during resuscitation (1) in the absence of effective hyperventilation or where carbon dioxide removal is inadequate despite adequate ventilation, (2) in repeated doses, without confirmation of substantial acidosis, or (3) when cardiac arrest has been of brief duration and preexisting acidosis is unlikely.

Level of Evidence 5 -Quality Fair - Opposing


Methods Prospective, randomized, blinded, crossover study. Fourteen adult patients who had metabolic acidosis (bicarbonate less than 17 mmol/L and base excess less than -10) and increased arterial lactate (mean, 7.8 mmol/L) received equimolar sodium bicarbonate and sodium chloride. All had pulmonary artery catheters and 13 were receiving catecholamines.

RESULTS: Sodium bicarbonate (2 mmol/kg body weight over 15 minutes) increased arterial pH (7.22 to 7.36, P < 0.001), serum bicarbonate (12 to 18 mmol/L, P < 0.001), and partial pressure of CO2 in arterial blood (PaCO2) (35 to 40 mm Hg, P < 0.001) and decreased plasma ionized calcium (0.95 to 0.87 mmol/L, P < 0.001). Comparable changes in pulmonary capillary wedge pressure and cardiac output was noted following infusion of both solutions.

CONCLUSIONS: Correction of acidemia using sodium bicarbonate does not improve hemodynamics in critically ill patients who have metabolic acidosis and increased blood lactate. Moreover, sodium bicarbonate administration did not improve the cardiovascular response to infused catecholamines in these patients. Sodium bicarbonate increased PaCO2
Comments: Small study. Strengths include randomized blinded and crossover.

Level of Evidence 5-Quality Good - Opposing


Background The effects of infusing a buffer solution on successful resuscitation and outcome was tested in patients during out-of-hospital cardiac arrest.

Methods A number (502) of adults with asystole or ventricular fibrillation with failure of first defibrillation attempt were entered into a prospective, randomized, double-blind, controlled trial. Of these, 245 patients received 250 ml of sodium bicarbonate-trometamol-phosphate mixture with buffering capacity 500 mmol/l and 257 patients received 250 ml 0.9% saline. Except for the investigational infusion, all patients were resuscitated according to international guidelines.

Results Eighty-seven patients (36%) receiving buffer were admitted to hospital ICU and 24 (10%) were discharged from hospital alive, vs. 92 (36%) and 35 (14%) receiving saline (95% confidence interval (CI) for difference between groups: -6%--6% for rate of admission and -1%-9% for rate of discharge). Using a logistic regression analysis, ventricular fibrillation as initial rhythm (odds ratio 8.06, CI 3.70-17.56) improved the outcome, whereas buffer therapy had no effect (odds ratio 0.77, CI 0.43-1.41). Mean base excess at hospital admission was -9 after Tribonat vs. -11 after saline (P = 0.04, CI for difference 0.2-3.8). Only 16 of the 502 patients had arterial alkalosis on arrival in the hospital and no patient had a positive base excess.

Conclusion Patients resuscitated after out-of-hospital cardiac arrest had metabolic acidosis, but buffer therapy did not improve the outcome.

Comments Randomized adult study of bicarbonate versus saline in asystolic out of hospital patient of whom one third in both groups were admitted to the ICU. Logistic modeling showed no improvement in outcome with buffer therapy. This is the only human randomized study addressing this specific question.

Level of Evidence 5-Quality Excellent - Neutral

Evidenced Based Review of Adult Clinical and Experimental Studies


This was an evidence based review that addressed the following question: what evidence supports the use of sodium bicarbonate in the therapy of acidosis associated with cardiac arrest during CPR.

Human studies (n=21)

Only one study Dyvik, T., T et al was prospective. As noted above, this study did not demonstrate a beneficial effect of buffer on ROSC or outcome after out of hospital cardiac arrest. (It was suggested that the study was underpowered and that it would take 4200 patients to show a difference.)

None of the retrospective studies showed any benefit, eight studies suggested a deleterious effect and 12 studies showed no difference. With regard to outcome 4 showed improved survival and 7 showed no difference. Regarding myocardial performance, none showed benefit, 12 were deleterious and 2 showed no difference.

The author’s conclusions included the following:

1) No human study has demonstrated a beneficial impact on survival
2) Several adult human studies (level 3 and 4) have demonstrated deleterious effects on physiologic end points from the administration of bicarbonate during CPR
3) Several animal studies have demonstrated impaired function in response to bicarbonate administration during CPR
4) Several animal studies (n=4) have demonstrated survival benefit from the administration of bicarbonate during CPR

Level of Evidence 5 -Quality Fair - Neutral

Adult Animal Studies


Objectives: To evaluate the effects of CO2 producing and non-CO2 producing buffers in a canine model of prolonged ventricular fibrillation followed by effective CPR.

Methods Prospective, randomized, controlled, blinded trial involving adult dogs (n=38). VF was electrically induced, and after 10 mins, CPR was initiated, including ventilation with an FIO2 of 1.0, manual chest compressions, administration of epinephrine (0.1 mg/kg every 5 mins), and defibrillation. A dose of buffer, equivalent to 1 mmol/kg of NaHCO3, was administered every 10 mins from start of CPR. Animals were randomized to receive either NaHCO3, Carbicarb, THAM, or 0.9% sodium chloride (NaCl). CPR was continued for up to 40 mins or until return of spontaneous circulation.

Results: Buffer-treated animals had a higher resuscitability rate compared with NaCl controls. Spontaneous circulation returned earlier and at a significantly higher rate after NaHCO3 (7/9 dogs), and after Carbicarb (6/10 dogs) compared with NaCl controls (2/10 dogs). Spontaneous circulation was achieved twice as fast after NaHCO3 compared with NaCl (14.6 vs. 28 mins, respectively). Hydrogen ion (H+) concentration and base excess, obtained 2 mins after the first buffer dose, were the best predictors of resuscitability. Arterial and mixed venous Pco2 did not increase after NaHCO3 or Carbicarb compared with NaCl.
Buffer therapy promoted successful resuscitation after prolonged cardiac arrest, regardless of coronary perfusion pressure. NaHCO3, and to a lesser degree, Carbicarb, was beneficial in promoting early return of spontaneous circulation. When epinephrine was used to promote tissue perfusion, there was no evidence for hypercarbic venous acidosis associated with the use of these CO2 generating buffers. This study demonstrated a positive benefit of sodium bicarbonate therapy.

**Level of Evidence 5- Quality Good- Supportive**


Objectives
To investigate the effect of different modes of sodium bicarbonate administration on blood gas parameters during CPR.

Methods
Adults dogs (n=36) were subjected to unassisted VF followed 10 minutes of CPR. Following 1 minute of CPR, the animals received one of four treatments in a randomized and blinded manner: normal saline (NS) (n=11), sodium bicarbonate bolus dose 1 mEq/kg (n=8), sodium bicarbonate continuous infusion 0.1 mEq/kg/min (n=8)(I), and sodium bicarbonate bolus dose (0.5 mEq/kg) plus continuous infusion 0.1 mEq/kg/min (n=9)(L + I).

Results
Following NS infusion, both arterial and venous pH declined consistently over time. Bolus NAHCO3 infusion had an elevated venous PCO2 (mm Hg) concentration following 6 minutes of ventricular fibrillation compared with NS, bolus and continuous NAHCO3 and continuous NAHCO3 groups (81 +/- 14 versus 69 +/- 10 versus 68 +/- 10 versus 71 +/- 8, respectively, (P = .07). Arterial pH and PCO2 values showed a similar trend as the venous data.

Comments
These observations suggest that if administration of sodium bicarbonate was contemplated a continuous infusion may be the most desirable mode of administration for the prevention of venous acidosis during CPR.

**Level of Evidence 5-Quality Good- Neutral**

Guerci, A. D.Chandra, N.Johnson, E. et al  Failure of sodium bicarbonate to improve resuscitation from ventricular fibrillation in dogs Circulation 1986;74(Suppl IV) 75-79

Objective
To determine the value of sodium bicarbonate in resuscitation from ventricular fibrillation and the prevention of spontaneous refibrillation.

Methods
Randomized placebo controlled study. Adult dogs (n=16) were administered sodium bicarbonate (1 meq/kg) or placebo 18 min after the induction of ventricular fibrillation and cardiopulmonary resuscitation. Defibrillation was attempted 2 min after the administration of bicarbonate or placebo.

Results
All animals were successfully defibrillated, but three of eight bicarbonate-treated and two of eight control animals died in electromechanical dissociation (p = NS). Spontaneous refibrillation occurred in three animals in each group (p = NS). Successful resuscitation was not dependent on treatment, arterial or mixed venous PCO2, or arterial or mixed venous pH but correlated strongly with coronary perfusion pressure (p < .003).

Comments
The data do not suggest a primary role for sodium bicarbonate in resuscitation following ventricular fibrillation in adult dogs. The relevance to the neonate who presents with bradycardia is unclear.

**Level of Evidence 5- Quality Fair- Neutral**


Objective
To determine the effect of bicarbonate administration on resuscitation in a porcine model of prolonged cardiac arrest.

Methods
Adult pigs (n=26) were subjected to ventricular fibrillation for 15 minutes (16 animals) or 20 minutes (ten animals) with no resuscitative efforts. Resuscitation attempts with open-chest cardiac massage and epinephrine were used in all animals after the arrest period. The experimental group was given sodium bicarbonate (3 mEq/kg), and the control group received 3% saline (5 mL/kg) at the initiation of cardiac massage.

Results:
There was no difference in resuscitation rates between bicarbonate and nonbicarbonate-treated swine. e. 6/8 bicarbonate-treated swine were resuscitated successfully compared with 5/8 hypertonic saline-treated animals. There was no difference in systolic or diastolic blood pressures or myocardial perfusion pressure between the bicarbonate and hypertonic saline-treated animals.

Comments
The use of sodium bicarbonate did not improve resuscitation from prolonged cardiac arrest.

**Level of Evidence 5-Quality Fair - Neutral**

Kette, F.Weil, M. H.Gazmuri, R. J. Buffer solutions may compromise cardiac resuscitation by reducing coronary perfusion pressure JAMA 1991;266:2121-6

Objective
To compare the infusion of sodium bicarbonate, Carbicarb and sodium chloride infusion on cardiac hemodynamics.

**OBJECTIVE:** To evaluate the hemodynamic actions of epinephrine combined with different buffer solutions during experimental open-chest resuscitation.

**Methods** Adult pigs (n=44) had cardiac arrest induced by ventricular fibrillation. Precordial compression was started at the third minute of untreated ventricular fibrillation and maintained for an interval of 8 minutes. A hypertonic solution of sodium bicarbonate, Carbicarb or an isotonic solution of sodium chloride was infused into the right atrium over a 1-minute interval starting at the sixth minute of ventricular fibrillation.

**Results** Infusion of hypertonic buffer and sodium chloride solutions increased plasma osmolality from an average of 280 to 330 mOsm/kg. This was accompanied by a significant decrease in the aortic pressures and CPPs generated during precordial compression. No such changes occurred after infusion of isotonic sodium chloride.

**Comments** Sodium bicarbonate solution in the absence of vasopressor agents may adversely affect cardiac resuscitation by reducing the coronary perfusion pressure below critical thresholds.

**Level of Evidence 5-Quality Fair**

**Objective** To determine whether administration of sodium bicarbonate and/or adrenaline in combination with a brief period of cardiopulmonary resuscitation (CPR) prior to defibrillation would improve the outcome of prolonged cardiac arrest in dogs.

**Methods** VF was induced and after 10 min of VF, animals (n=24) received either immediate defibrillation (followed by treatment with bicarbonate or control) or immediate treatment with bicarbonate or saline (followed by defibrillation).

**Results** Blood flow measured in the pulmonary artery during open-chest CPR was approximately 20% of normal cardiac output. Administration of epinephrine reduced pulmonary artery flow irrespective of buffer. Sodium bicarbonate alone resulted in higher systemic blood pressure than pure tris: tris buffer mixture and normal saline were intermediate. Sodium bicarbonate combined with epinephrine tended to produce lower systemic blood pressure than other combinations.

**Comments** These data suggest that following prolonged arrest, bicarbonate therapy and a period of perfusion prior to defibrillation may increase survival. However, longer-term outcome and in particular CNS outcome is not provided. There is biochemical, histological and clinical evidence that the cumulative energy dose delivered to the myocardium during defibrillation attempts is associated with myocardial damage, which decreases the likelihood of successful resuscitation. This is not a concern to the neonatal population.

**Level of Evidence 5-Quality Fair**

**Objective** To determine the impact of EPI and NaHCO3 given during CPR on long term outcome.

**Methods** Sprague-Dawley rats (n=100) were prospectively studied in a block randomized placebo controlled trial. Each rat underwent 10 min of asphyxia, resulting in 6.8 +/- 0.4 min of circulatory arrest. Resuscitation was performed by mechanical ventilation and manual external chest compressions. EPI 0.0 (placebo), 0.01, 0.1, or 1.0 mg/kg IV was given at the onset of CPR, followed by NaHCO3 0.0 (placebo) or 1.0 mEq/kg IV. Neurologic deficit scores (NDS), cerebral histopathologic damage scores (CHDS) and myocardial histopathologic damage scores (MHDS) were determined in rats that survived 72 h.

**Results** EPI improved CoPP and ROSC in a dose-dependent manner up to 0.1 mg/kg. Rats receiving EPI 0.1 and 1.0 mg/kg during CPR exhibited prolonged post-ROSC hypertension and metabolic acidemia, increased A-a O2 gradient, and an increased incidence of post-ROSC ventricular tachycardia or fibrillation. Overall survival was lower with EPI 0.1 and 1.0 mg/kg compared to 0.01 mg/kg.

**Comments** Although NDS was significantly less with EPI 0.1 mg/kg compared to placebo, there was no difference in CHDS between groups. In contrast, MDS was significantly higher with EPI 0.1 mg/kg compared to placebo or EPI 0.01 mg/kg. There was an overall trend toward improved survival at 72 h in rats that received NaHCO3 which was most evident in the EPI 0.1 mg/kg group.
reported (25% to 40% of normal cardiac output) from studies of closed-chest CPR. Different alkaline buffers influence circulatory and acid-base parameters differently before and after administration of epinephrine.

Comments Combination of high dose epinephrine and sodium bicarbonate produced lower systemic blood pressure

**Level of Evidence 5-Quality Fair - Supportive**


Objective: To determine the effects of bicarbonate therapy on outcome in a canine model of ventricular fibrillation cardiac arrest of brief (5-min) and prolonged (15-min) duration.

Methods Prospective, randomized, controlled trial involving adult dogs (n=32). VF was induced and maintained in arrest for 5 mins (n = 12) or 15 mins (n = 20). Canine advanced cardiac life-support protocols were instituted, including defibrillation, cardiopulmonary resuscitation (CPR), and the administration of epinephrine (0.1 mg/kg), atropine, and lidocaine. The bicarbonate group received 1 mmol/kg of sodium bicarbonate initially, and base deficit was corrected to -5 mmol/L with additional bicarbonate, whereas acidemia was untreated in the control group. A neurologic deficit score was determined at 24 hrs after CPR.

Results The treatment group received an additional 2 to 3 mmol/kg of bicarbonate in the early postresuscitation phase. Compared with controls, the bicarbonate group demonstrated equivalent (with brief arrest) or improved (with prolonged arrest) return of spontaneous circulation and survival to 24 hrs, with lessened neurologic deficit. The acidosis of arrest was decreased in the prolonged arrest group without hypercarbia. Improved coronary and systemic perfusion pressures were noted in the bicarbonate group with prolonged arrest, and the epinephrine requirement for return of spontaneous circulation was decreased.

Comments The empirical administration of bicarbonate improves the survival rate and neurologic outcome in a canine model of cardiac arrest. These observations support the current recommendation of sodium bicarbonate administration following prolonged resuscitation in the face of adequate ventilation

**Level of Evidence 5-Quality Fair - Supportive**

Wiklund, L.Ronquist, G.Stjernstrom, H. Waldenstrom, A Effects of alkaline buffer administration on survival and myocardial energy metabolism in pigs subjected to ventricular fibrillation and closed chest CPR Acta Anaesthesiol Scand 1990;34: 430-439

Objective To determine the effects of alkaline buffer administration on survival and myocardial energy metabolism

Methods Anesthetized piglets (n=19) were investigated. VF was induced followed by a 10-min period of cardiopulmonary resuscitation (CPR) i.e. manual chest compression and mechanical ventilation with pure oxygen. After 1 min of CPR an infusion of alkaline buffer was begun and was completed within 5 min. A total of 50 mmol of one of two different buffer solutions was given, either sodium bicarbonate (n = 6) or tris buffer mixture (n = 7). These two groups were compared with a third control group (n = 6) receiving the same volume of normal saline. After 8 min of CPR all animals were given 0.5 mg adrenaline i.v., Myocardial biopsies were then taken immediately in all animals.

Results Successful CPR was more frequent in the animals given normal saline or tris buffer mixture and no effect was seen in the group given sodium bicarbonate. Survival was statistically correlated to low myocardial content of creatine phosphate and low base excess values in blood. Such parameters as myocardial content of ATP or ACP (adenylate charge potential) had no direct correlation to survival. Sodium bicarbonate induced significantly higher base excess and PCO2 values, while the tris buffer mixture seemed to have a greater alkalinizing effect intracellularly.

Comments Sodium bicarbonate infusion was associated with higher PCO2 .

**Level of Evidence 5-Quality Fair - Opposing**