The Use (or non-use) of sodium bicarbonate to treat neonatal metabolic acidosis

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Overview and objectives

- Objective evidence lacking that administration of sodium bicarb improves outcomes for patients in cardiopulmonary arrest or with metabolic acidosis
- There is evidence that this therapy is detrimental
- Review history of sodium bicarb use in neonatology
- Review evidence that refutes the clinical practice of administering sodium bicarb during CPR or to treat metabolic acidosis in the NICU
(False) rationale for use of bicarb in cardiopulmonary arrest

- Premise that acidemia impairs myocardial performance and attenuates blood pressure, heart rate, and cardiac contractility in response to catecholamines
- However, clinical and animal studies show that it does not improve outcomes
- There is increasing evidence that it is detrimental to myocardial function and reduces the likelihood of successful resuscitation
Animal studies and use of bicarb during CPR

- Bicarb for lactic acidosis decreased cardiac output and BP in dogs (Graf, 1985)
- Bicarb corrected arterial metabolic acidosis, but led to a decrease in intramyocardial pH and reduced the likelihood of successful resuscitation (Kette, 1990)
- Hypertonic solutions, such as bicarb, affected cardiac resuscitation adversely by reducing coronary perfusion pressure (Kette, 1991)
- 1998 review by Levy summarizing > 30 studies
  - Of studies with survival as the outcome, 4 showed benefit, 7 did not
  - When myocardial performance was assessed
    - 12 showed worse myocardial performance
    - 2 showed no difference
    - 1 showed no benefit
Publications dating back to the 1970s have demonstrated that giving bicarb during CPR causes hypernatremia, hyperosmolality, and metabolic alkalosis.

Both metabolic alkalosis and hyperosmolality after CPR associated with increased mortality rates.

1 prospective RCT of bicarb use in adults after cardiac arrest; failed to show a benefit in return of spontaneous circulation or in survival rates.

19 retrospective adult studies examining mortality rates:
- 0 demonstrated benefit
- 11 showed no difference
- 8 suggested a deleterious effect
Neonatal studies

- Only 1 RCT of sodium bicarbonate use in neonates has been published (Lokesh, 2004)
  - 55 newborn infants with asphyxia who required assisted ventilation at 5 minutes after birth
  - No benefit of bicarb in mortality or abnormal neuro exam at discharge (no long-term follow-up)

- To date, there have been no human studies in any age group demonstrating a beneficial effect of bicarb on survival rates after cardiac arrest
Biochemical basis for harmful effects during cardiac arrest

- Infusion of sodium bicarbonate results in the immediate formation of CO2 in equimolar amounts
- In the early cardiopulmonary arrest, minute ventilation and pulmonary blood flow are low
- Henderson-Hasselbach equation
  \[ \text{pH} = pK_1 + \log \left[ \frac{[\text{HCO}_3^-]}{[\text{CO}_2]} \right] \]
  \( (pK_1 = 6.1) \)
- To get pH 7.4, \([\text{HCO}_3^-]/[\text{CO}_2]\) molar ratio must be 20:1!
Biochemical basis for harmful effects during cardiac arrest

- Giving bicarb to a patient with inadequate ventilation causes worsening acidosis, CO2 accumulation and a shift of the H-H equation to the left.
- CO2 diffuses across cell membranes leading to intracellular acidosis (causing impairment of cellular function), whereas the bicarb lags behind in the vascular space, leading to metabolic alkalosis.
2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: international consensus on science, published in Pediatrics

- There are “insufficient data to recommend routine use of bicarbonate in resuscitation of the newly born…the hyperosmolarity and CO$_2$-generating properties of sodium bicarbonate may be detrimental to myocardial or cerebral function.”

2005 AHA guidelines for CPR no longer recommend therapy with buffers during cardiac arrest

- lack of evidence that bicarbonate improves the likelihood of successful defibrillation or survival rates
AHA guidelines: adverse effects of bicarb during cardiopulmonary arrest

(1) Compromising coronary perfusion pressure by reducing systemic vascular resistance

(2) Creating extracellular alkalosis, which shifts the oxyhemoglobin saturation curve and inhibits $O_2$ release to the tissues

(3) Producing hypernatremia and hyperosmolarity, both of which have been associated with increased mortality rates

(4) Producing excess $CO_2$, which freely diffuses into myocardial and cerebral cells and paradoxically may contribute to intracellular acidosis

(5) Exacerbating central venous acidosis, which paradoxically may inactivate simultaneously administered catecholamines
Additional AHA guidelines

- ABG monitoring during cardiac arrest is not a reliable indicator of the severity of tissue hypoxemia, hypercarbia, or tissue acidosis.
- Mainstays of acid-base balance restoration during cardiac arrest:
  - Restoration of oxygen content with appropriate ventilation with oxygen.
  - Support of tissue perfusion and cardiac output with good chest compressions.
  - Then rapid return of spontaneous circulation.
Facts for neonatal metabolic acidosis

- pH < 7.3 with low bicarb and normal or low P_{CO2}
- Due to one of 3 mechanisms
  - Loss of base via renal or GI routes
  - Intake of more acid than the kidneys can excrete
    - High-protein diet
    - Renal insufficiency
  - Abnormal metabolism resulting in endogenous acid levels
    - Inorganic acids (eg, nitrates, sulfates, and phosphates) from rapid tissue catabolism in very ill patients
    - Organic acids from incomplete oxidation of fuels (eg, lactate, acetoacetate, and methylmalonate)
Late metabolic acidosis of prematurity

- Increase in H⁻ concentration from intake > renal clearance from immature kidneys
- Urinary pH usually < 5.5, growth impairment
- More common from old casein-based formulas, still can be seen from TPN
- Giving base such as acetate in HA, sodium citrate or dilute sodium bicarb may be appropriate
  - Even under these circumstances, however, the efficacy and safety of sodium bicarbonate replacement therapy have not been proven!
Cochrane reviews: insufficient evidence to use bicarb

- Base administration or fluid bolus for preventing morbidity and mortality in preterm infants with metabolic acidosis (Lawn, 2005): 2 small RCTs
  - 1977 trial of bicarb in preterm infants (N = 30) vs no treatment (N = 32)—all received IV glucose and water
    - No decrease in morbidity (IVH) and mortality and the pH corrected as quickly in either group
    - No long-term outcomes reported
  - 1995 comparison of bicarb vs albumin fluid boluses in 36 infants with metabolic acidosis
    - Bicarb group had higher arterial pH values, lower base excess at 2 hours after intervention
    - No other clinical outcomes reported
Cochrane reviews: insufficient evidence to use bicarb

- Sodium bicarbonate infusion during resuscitation of infants at birth (Beveridge, 2005): 1 RCT
- Asphyxiated newborn infants (PPV at 5 minutes after birth) treated with bicarb (N = 27) vs D5W (N = 28)
- No effect on:
  - Mortality
  - Abnormal neurological exam at d/c
  - Composite outcome of death or abnormal neuro exam at d/c
  - Incidence of encephalopathy
  - IVH
  - Seizures
- No long term neurodevelopmental outcomes assessed
Cochrane reviews: insufficient evidence to use bicarb

- Rapid correction of early metabolic acidemia in comparison with placebo, no intervention or slow correction in LBW infants (Kecskes, 2002)

- No studies were found meeting the criteria for inclusion in this review
Evidence for harm in neonates

- Large bicarb infusions to correct acidemia in premature infants are associated with increased mortality and IVH (Usher, 1967; several other studies)

- Rapid vs slow bolus of bicarb to preterm infants showed more pronounced increases in cerebral blood volume seen using NIRS (van Alfen-van der Velden, 2006)

- Bicarb causes myocardial injury in young children with chronic renal failure (Lipshultz, 2003; also other studies in children with acute renal failure)
Acetate use?

- No studies available for outcomes with “chronic” use of buffers like sodium acetate

- RCT of acetate in preterm neonates receiving TPN from days 3-10, enrolled if NPO on day 3 (Peters, 1997)
  - 58 neonates < 32 weeks given “standard” chloride-based TPN vs replacement of Cl⁻ as acetate, for any Cl⁻ > 3 mmol/kg/day
  - Acetate
    - Decreased the incidence of hyperchloremia from 77% to 25%
    - Increased base excess difference from day 5 onwards from 3.6 to 9.9 mmol/L
    - Increased pH (on day 8) 7.26 vs 7.34
    - Increased pCO2 difference by 1 kPa
    - Acetate group received less bicarb and less colloid
    - No difference in assisted ventilation parameters or inotropes
    - Other outcomes not studied
Acetate use: theoretic effects

- Preterm infants may have poor tissue and renal perfusion, contributing to acidosis
- Volume expanders and inotropes have been used to “treat” this in the past, with no improvement in outcomes when actually studied
- Preterm kidneys are functionally immature, with excess Na+ loss and failure to acidify urine
- Giving additional dietary Na+ leads to excess Cl⁻ administration and hyperchloremia
- Hyperchloremia associated with metabolic acidosis
Acetate use: theoretic effects

- Acidosis is thought to be a causative factor in IVH and pulmonary hypertension
- Since acidosis is usually mixed (resp + metabolic), respiratory interventions might be used to overcome a metabolic problem and lead to lung damage
- Acetate administration makes the numbers look “better”
THAM use?

- No trials/studies available for outcomes with THAM in neonates
- THAM is associated with the 3rd highest mortality rate in a list of the top 20 NICU drugs for which the patient population had a > 20% mortality rate (Clark, 2005)
  - THAM = 36% mortality (died/overall discharges) or 46% mortality (died/died+home)
  - N = 565 for THAM use
Conclusions

- The data do not support a net beneficial effect of sodium bicarbonate in infants with metabolic acidosis.
- An unproven exception may be the replacement of base for ongoing renal or GI losses.
- Adverse effects associated with the use of sodium bicarbonate include:
  - fluctuations in cerebral blood flow
  - intracranial hemorrhage
  - diminished oxygen delivery to tissues
  - worsening intracellular acidosis
  - aggravated myocardial injury
  - deterioration of cardiac function
Conclusions

- Current published recommendations for dose, dilution, and rate of administration are largely arbitrary
- Appropriately powered RCTs of sodium bicarbonate therapy to treat metabolic acidosis in NICU patients needed
- Instead of giving bicarb, we should try to understand and treat the underlying cause of the acidosis
Proposal

- Discontinue the use of sodium bicarbonate to treat neonates for metabolic acidosis
- Exceptions may potentially include replacement of ongoing GI or renal losses of bicarb, specific metabolic disorders, emergent treatment of hyperkalemia, but benefits are unproven even in these settings
References

- Sodium Bicarbonate: Basically Useless Therapy. Aschner, Judy L. and Poland, Ronald L. Pediatrics 2008;122;831-835