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Management of Neonatal Emergencies: Current Evidence from Cochrane/ other Systematic Reviews

Clinical Question: Sodium Bicarbonate in Neonatal Resuscitation and Cardiac Arrest: Constructive or Destructive

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Abstract

In this era of evidence based practice, there are therapies which still continue to be used despite lack of evidence supporting their use. One of them is the use of bicarbonate therapy in newborn resuscitation and cardiac arrest. Sodium bicarbonate has been used for many years to treat neonatal cardiac arrest and metabolic acidosis. Both animal studies and human studies have however failed to provide any benefit associated with bicarbonate administration. In this article we have briefly reviewed the evidence pertaining to the use of this drug in newborn resuscitation which may be serve as a useful tool to the newborn community to decide for or against using this drug in their day-to-day practice.

Key words: Sodium bicarbonate; Newborn; Metabolic acidosis; Cardiac arrest; Resuscitation.

Case scenario

You have been called to the labor room to help resuscitate a term infant to be born by forceps vaginal delivery.

The neonate had significant bradycardia even after positive pressure ventilation and chest compression. You plan to give normal saline bolus and your resident orders for sodium bicarbonate to the staff. You are not convinced on giving sodium bicarbonate. Your resident questions you as to why you are not convinced in giving sodium bicarbonate? You tell him that you will discuss the evidence of using this medication for resuscitation of newborns after reviewing the literature once again.

You are now confronted with the following questions:

1. Is sodium bicarbonate at all useful for neonatal resuscitation or cardiac arrest?

2. What is the mechanism of action of sodium bicarbonate in cardiac arrest?

3. Are there any studies available that have compared use of sodium bicarbonate vs. no bicarbonate in neonatal resuscitation?

4. Is there any need to change my practice of not giving sodium bicarbonate?

You inform him that you will answer his query after reviewing the available literature.

Clinical question

Does sodium bicarbonate help in resuscitation or cardiac arrest in neonates?

Background

Sodium bicarbonate has long been used in neonatal resuscitation and cardiac arrest. The scientific rationale for use in cardiac arrest is that acidemia impairs myocardial function and reduces the beneficial effects of inotropes on heart rate, blood pressure and cardiac output[1]. Correction of acidosis by buffer agents such as sodium bicarbonate given during cardiac arrest may help by reversing this acidosis[2,3]. But the evidence available form adult and neonatal studies points toward a detrimental effect with its use. Thus the debate still continues on giving sodium bicarbonate in neonatal resuscitation and cardiopulmonary arrest. In this article we have tried to attempt evidence based review on use of sodium bicarbonate in neonates with cardiopulmonary arrest which would help clinician to take wise decision in use of this drug for compromised neonates.

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Evidence for use of sodium bicarbonate in cardiopulmonary arrest

As of today there are limited neonatal studies on this subject , including a randomized study and a cochrane review.

Cochrane review

The cochrane review [4] (2006) by Beveridge and Wilkinson, included only one high quality study from India[5] (Lokesh 2004). This study enrolled 55 asphyxiated neonates (infants continuing to need positive pressure ventilation at 5 minutes after birth) and compared treating them with sodium bicarbonate infusion (n = 27) versus 5% dextrose (n = 28). The study group was given intravenous sodium bicarbonate solution, diluted in 1:1 with distilled water, 4 ml/kg (1.8 meq./kg) over 3–5 min. The results revealed no evidence of an effect on mortality prior to discharge [relative risk (RR) 1.04 (95% 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% CI 0.59 to 1.60)]. There was no statistically significant difference in the incidence of encephalopathy [RR 1.30 (95% CI 0.88 to 1.92)], intraventricular haemorrhage [RR 1.04 (95% CI 0.23 to 4.70)] and neonatal seizures [RR 1.19 (95% CI 0.50 to 2.82)]. This study, however, did not report the long term neurodevelopmental outcome.

Observational trials

Berg C.S et al[6], in a recently published study, analysed 984, VLBW neonates on use of sodium bicarbonate in NICU over a period of four years (2002-2006). Out of the 984 neonates 166 required sodium bicarbonate infusion in first seven days of life. In this retrospective study, sodium bicarbonate infusion was associated with an increased risk of death or intraventricular hemorrhage (OR 2.14, 95% CI 1.65-2.77, P < .001). Even after adjustment for potential confounders (birth year, gestational age, sex, sickness score, pneumothorax, hypercarbia, red blood cell transfusion volume, highest sodium in the first 7 days of life), sodium bi-carbonate infusion remained associated with an increased risk of death and intraventricular hemorrhage (OR 1.27, 95% CI 1.05-1.49, P = .01). They found minimal change in pH measured after sodium bicarbonate infusion. However, they did report a significant increase in bicarbonate levels, suggesting a concurrent increase in CO_2 levels.

Similar observations of increase in intraventricular haemorrhage following bicarbonate infusion have been reported in other studies in early literature. [7 8]

Adult studies

Randomized controlled trials

There has been only one prospective, randomized, controlled trial of sodium bicarbonate use in adults after cardiac arrest. That study failed to show a benefit of sodium bicarbonate in return of spontaneous circulation or in survival rates. [9]

Retrospective studies

Till date there have been ninteen retrospective adult studies reporting mortality and short term outcomes, none of the studies demonstrated benefit, eleven showed no difference in outcomes, and 8 suggested a deleterious effect of administering sodium bicarbonate during cardiopulmonary resuscitation. [1011]

Animal Data

Levy et al[10] in 1998 reported the animal data from 30 animal studies evaluating the efficacy of sodium bicarbonate administration during CPR. None of the studies showed benefit in terms of cardiac performance as assessed by echocardiography, rather few studies reported detrimental effect on myocardial contractility. Although 4 studies did report a beneficial effect in terms of mortality, but all other studies (eleven) reported a worst outcome.

Biochemical basis for harmful effects during cardiac arrest

Being an old age therapy still there is lack of evidence in support of sodium bicarbonate in neonatal and adult cardiac arrest. Let us understand the basics of acid balance involving the external administration of sodium bicarbonate which makes it as a "useless therapy" in cardiac arrest despite being an excellent base buffer**.** Aschner and Poland[11] have given an excellent biochemical explanation for the same.

Let us start from the Henderson-Hasselbach equation which states that pH = pK1 + log $[HCO_3]/ [CO_2]$ where pK1=6.1. According to this equation the pH depends on the ratio of HCO_3 and CO_2 present in the blood. It is also known that, for any biological buffer system, optimal buffering occurs when pH and pK are within 1 pH unit of each other. The greater the gap between pK and the target pH value, the less effective is the buffer. The apparent pK of this "buffer" is 6.1, well outside the optimal buffering range of the normal blood pH of 7.4. (The pK is determined as the pH at which the relevant salt and acid concentrations, in this case the molar concentrations of HCO3 and CO2, are equal). Therefore, the bicarbonate system can buffer an acid load effectively only when the lungs can remove excess carbon dioxide from the blood effectively. When impaired ventilation brings the HCO_3 /CO_2 ratio closer to 1:1, addition of sodium bicarbonate moves the pH toward the apparent pK of 6.1. When sodium bicarbonate is given to a neonate it results in formation of carbon dioxide. For every 1 mol of hydrogen ion neutralized by bicarbonate, an equimolar amount of carbon dioxide is produced (equation 1). The carbon dioxide generated diffuses rapidly across cell membranes to equilibrate between intracellular and extracellular compartments, leading to intracellular acidosis, whereas the bicarbonate lags behind in the vascular space, leading to metabolic alkalosis. [12]

$H^+ + HCO_3^-$ "! H_2CO_3 "! $H_2O + CO_2$ (the CO_2 produced diffuses rapidly inside the cell)

Equation 1: Bicarbonate/CO_2equilibruim

In the early minutes of a cardiopulmonary arrest, both minute ventilation and pulmonary blood flow are low. So from this discussion we really need to know is what is happening intracellularly; (1) Intra-mitochondrial acidosis alters energy production; (2) Intra-cardiac acidosis alters cardiac function; (3) Intra-brain acidosis produces fluctuations in cerebral blood flow[13]. During CPR, even with optimal ventilation, decreased cardiac output persists. Intracellular acid accumulates because of venous hypercarbia. However, arterial and end-tidal carbon dioxide levels may be normal or low.[14] Therefore, the intracellular acidosis associated with the use of sodium bicarbonate may not be reflected in the arterial blood gas values that are so closely monitored and relied on by clinicians during and after cardiac arrest.

To conclude the biochemical basis, bicarbonate can act as a physiological buffer only in an open system in which CO_2 can be eliminated from lungs. If CO_2 cannot be eliminated, it leads to intravascular and intracellular acidosis. The intracellular acidosis occurs because CO_2 can diffuse rapidly across cell membranes compared to bicarbonate [12]. So, following bicarbonate administration, CO_2 may accumulate at tissue level and can induce a paradoxical tissue and intracellular hypercarbia, hence acidosis despite improved arterial pCO_2 [14]

Conclusion

The assumption that correction of acidemia by infusion of sodium bicarbonate improves the outcome has not been documented till date. To the contrary, there is increasing evidence that it may be counterproductive[15]. We have already understood as stated above that sodium bicarbonate can lead to paradoxical neuronal acidosis if CO_2 elimination is not effective. This intervention accounts for iatrogenic increases in plasma levels of sodium, hyperosmolality of plasma, and metabolic alkalosis. A review by Hein et al [15] on use of bicarbonate in neonatal resuscitation concluded that the treatment is more likely to lead to problems such as intracellular acidosis[16 17], rather than to facilitate

resuscitation. The neonatal resuscitation guidelines[18] from the American Heart Association committee no longer recommend bicarbonate as a therapy in neonatal resuscitation. With lack of evidence for any beneficial effects, such therapy should be seen as ''basically useless therapy".[11]

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