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Sodium Bicarbonate: Basically Useless Therapy

Judy L. Aschner, MD^{a,b,c}, Ronald L. Poland, MD^d

^aDepartment of Pediatrics, ^bCenter for Molecular Toxicology, and ^cVanderbilt Kennedy Center for Research on Human Development, Vanderbilt University Medical Center, Nashville, Tennessee; ^dDepartment of Pediatrics, University of New Mexico Health Sciences Center, Albuquerque, New Mexico

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ABSTRACT

Common clinical practices often are unsupported by experimental evidence. One example is the administration of sodium bicarbonate to neonates. Despite a long history of widespread use, objective evidence that administration of sodium bicarbonate improves outcomes for patients in cardiopulmonary arrest or with metabolic acidosis is lacking. Indeed, there is evidence that this therapy is detrimental. This review examines the history of sodium bicarbonate use in neonatology and the evidence that refutes the clinical practice of administering sodium bicarbonate during cardiopulmonary resuscitation or to treat metabolic acidosis in the NICU. *Pediatrics* 2008;122:831–835

SODIUM BICARBONATE HAS been used in clinical medicine since the late 1950s. Given the long and pervasive practice of administering sodium bicarbonate to patients of all ages, one would hope that the evidence to support its use is well substantiated in the literature. Unfortunately, the evidence supporting the use of sodium bicarbonate in any clinical context is far from compelling. The rationale for its use in cardiopulmonary arrest was based on the premise that acidemia impairs myocardial performance and attenuates blood pressure, heart rate, and cardiac contractility in response to catecholamines. Therefore, clinicians have been taught to correct acidosis with sodium bicarbonate before giving epinephrine during cardiopulmonary resuscitation (CPR). However, the assumption that correction of acidemia through infusion of sodium bicarbonate improves CPR outcomes has been refuted by clinical and animal studies. To the contrary, there is increasing evidence that this once-common practice is detrimental to myocardial function and reduces the likelihood of successful resuscitation.¹

LACK OF EVIDENCE FOR EFFICACY AND POTENTIAL FOR HARM DURING CARDIAC ARREST

Doubts about the value of sodium bicarbonate infusion during cardiac arrest date back to the 1980s. In 1985, Graf et al² reported that cardiac output and blood pressure decreased more quickly in dogs breathing a hypoxic gas mixture when sodium bicarbonate was used to treat their lactic acidosis. In 1990, Kette et al³ showed that, although sodium bicarbonate corrected arterial metabolic acidosis, it led to a decrease in intramyocardial pH and reduced the likelihood of successful resuscitation. In a follow-up article in 1991, the same group showed that hypertonic solutions, such as sodium bicarbonate, affected cardiac resuscitation adversely by reducing coronary perfusion pressure.⁴ Coronary perfusion pressure, defined as aortic pressure minus right atrial pressure, has been shown to be an important determinant of successful cardiac resuscitation. Compared with animals given isotonic saline solution, those given hypertonic saline solution or sodium bicarbonate had a lower coronary perfusion pressure and were far less likely to be resuscitated successfully after cardiac arrest.⁴ A 1998 review article by Levy⁵ summarized the results of >30 animal studies evaluating the efficacy of sodium bicarbonate administration during CPR. Among studies with survival as the primary outcome, 4 showed benefit and 7 did not. When myocardial performance was assessed, 12 studies concluded that administration of sodium bicarbonate during CPR worsened myocardial performance, 2 studies showed no difference, and no study demonstrated benefit.⁵

Studies with human patients also challenge the benefits of sodium bicarbonate administration during cardiac arrest. Publications dating back to the 1970s have demonstrated that the administration of sodium bicarbonate during CPR causes hypernatremia, hyperosmolality, and metabolic alkalosis.⁶ Both metabolic alkalosis and hyperosmolality after CPR have been associated with increased mortality rates.^{6,7} Regrettably, there has been only 1 prospective, randomized, controlled trial (RCT) of sodium bicarbonate use in adults after cardiac arrest.⁸ That study failed to show a benefit of sodium bicarbonate in return of spontaneous circulation or in survival rates. Among 19 retrospective adult studies examining mortality rates and other outcomes, none demonstrated benefit, 11 showed no difference in outcomes, and 8 suggested a deleterious effect of sodium bicarbonate administration during CPR.⁵ Equally distressing, only 1 RCT of sodium bicarbonate use in neonates has been published.⁹ That trial of 55 newborn infants with asphyxia who required assisted ventilation at 5 minutes after birth found no benefit of sodium bicarbonate in

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Key Words

sodium bicarbonate, metabolic acidosis, neonatal resuscitation, NICU, clinical practice

Abbreviations

CPR—cardiopulmonary resuscitation
RCT—randomized, controlled trial

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Address correspondence to Judy L. Aschner, MD, Vanderbilt Children's Hospital, Neonatology, 11111 Doctor's Office Tower, 2200 Children's Way, Nashville, TN 37232-9544. E-mail: judy.aschner@vanderbilt.edu

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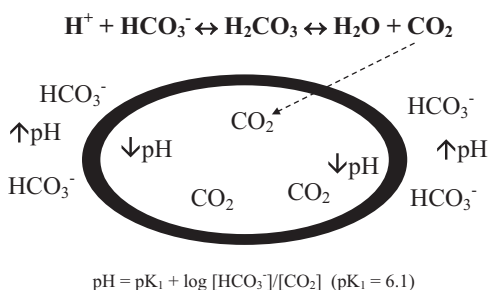


FIGURE 1

Fate of carbon dioxide (CO_2) after administration of sodium bicarbonate. The oval indicates the cell membrane.

mortality rates or rates of abnormal neurologic examination results at discharge. No long-term neurodevelopmental outcomes were assessed.^{9,10} To date, there have been no human studies in any age group demonstrating a beneficial effect of sodium bicarbonate on survival rates after cardiac arrest.

BIOCHEMICAL BASIS FOR HARMFUL EFFECTS DURING CARDIAC ARREST

As noted by Singer et al¹¹ in 1956, infusion of sodium bicarbonate results in the immediate formation of carbon dioxide. For every 1 mol of proton neutralized by bicarbonate, an equimolar amount of carbon dioxide is produced (Fig 1). In the early minutes of a cardiopulmonary arrest, both minute ventilation and pulmonary blood flow are low. The futility of using sodium bicarbonate in a situation in which carbon dioxide cannot be readily eliminated can be appreciated with the Henderson-Hasselbalch equation, $\text{pH} = \text{pK}_1 + \log [\text{HCO}_3^-]/[\text{CO}_2]$ ($\text{pK}_1 = 6.1$). This equation shows that 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 HCO_3^- and CO_2 , 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 $\text{HCO}_3^-/\text{CO}_2$ ratio closer to 1:1, addition of sodium bicarbonate moves the pH toward the apparent pK of 6.1. In fact, to achieve a pH value of 7.4, the $\text{HCO}_3^-/\text{CO}_2$ molar ratio must be 20:1.¹

From this discussion, it follows that administration of sodium bicarbonate to a patient with inadequate minute ventilation would cause worsening acidosis, with carbon dioxide accumulation and a shift of the Henderson-Hasselbalch equation to the left. 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

alkalosis¹ (Fig 1). The negative consequence is an immediate decrease in intracellular pH and impairment of cellular function.

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.¹² 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.¹² Given the chemical facts, it is not surprising that many controlled clinical studies of bicarbonate administration have failed to show benefit and several have documented harm.

CONCLUSIONS ON USE OF SODIUM BICARBONATE DURING CPR

Data for adults and neonates do not support the administration of buffers during cardiac arrest. Deleterious effects on myocardial performance after administration of bicarbonate during CPR were reported in several adult human studies, whereas no human study has demonstrated a beneficial impact of bicarbonate on survival rates. Because objective evidence fails to establish that the benefits of sodium bicarbonate outweigh the risks, changes were made to the neonatal resuscitation guidelines issued at the Guidelines 2000 Conference.¹³ There are "insufficient data to recommend routine use of bicarbonate in resuscitation of the newly born."¹³ The guidelines further state, "In fact, the hyperosmolality and CO_2 -generating properties of sodium bicarbonate may be detrimental to myocardial or cerebral function."¹³ Similarly, the 2005 American Heart Association guidelines for CPR no longer recommend therapy with buffers during cardiac arrest, noting lack of evidence that bicarbonate improves the likelihood of successful defibrillation or survival rates.¹⁴ These guidelines expound on the adverse effects linked to bicarbonate administration during cardiac arrest, which include (1) compromising coronary perfusion pressure by reducing systemic vascular resistance; (2) creating extracellular alkalosis, which shifts the oxyhemoglobin saturation curve and inhibits oxygen release to the tissues; (3) producing hyponatremia and hyperosmolality, both of which have been associated with increased mortality rates; (4) producing excess carbon dioxide, which freely diffuses into myocardial and cerebral cells and paradoxically may contribute to intracellular acidosis; and (5) exacerbating central venous acidosis, which paradoxically may inactivate simultaneously administered catecholamines. The American Heart Association guidelines warn that arterial blood gas monitoring during cardiac arrest is not a reliable indicator of the severity of tissue hypoxemia, hypercarbia, or tissue acidosis, and they admonish us to recall that restoration of oxygen content with appropriate ventilation with oxygen, support of tissue perfusion and cardiac output with good chest compressions, and then rapid return of spontaneous circulation are the mainstays of acid-base balance restoration during cardiac arrest.¹⁴

"BASIC" FACTS ON USE FOR NEONATAL METABOLIC ACIDOSIS

Metabolic acidosis is a common finding in NICUs, and administration of sodium bicarbonate is a common response to a blood gas sample with a low pH. Although depression of intracellular pH can have adverse effects on cell function, several natural defense mechanisms help maintain a narrow range of intracellular pH values in the presence of dramatic extracellular metabolic acidosis.¹⁵ Before treating a laboratory value, it is important to consider the underlying cause and whether the treatment might be worse than the problem it is meant to correct. A growing body of literature warns of potential adverse effects of sodium bicarbonate administration and challenges the efficacy of such treatment.¹²

What follows is a brief overview of mechanisms leading to metabolic acidosis and some of the associated clinical conditions. This is followed by current evidence about the potential risks and questionable benefits of bicarbonate therapy.

Acidosis is the process leading to an abnormally high concentration of hydrogen ions; acidemia refers to an abnormally low pH in the blood. Metabolic acidosis is diagnosed when the blood pH is below 7.30 with a low bicarbonate concentration and a normal or low P_{CO_2} . Metabolic acidosis is the consequence of 1 of 3 fundamental mechanisms, that is, (1) loss of base via renal or gastrointestinal routes, (2) intake of more acid than the kidneys can excrete (eg, high-protein diet or renal insufficiency), or (3) abnormal metabolism resulting in increased endogenous acid levels, with inorganic acids (eg, nitrates, sulfates, and phosphates) from rapid tissue catabolism in very ill patients or organic acids from incomplete oxidation of fuels (eg, lactate, acetoacetate, and methylmalonate).

Bicarbonate loss can be the result of renal tubular acidosis or chronic diarrhea.^{16,17} In both cases, hyperchloremia is common, hypokalemia may occur, and the serum anion gap, defined as $[Na^+] - ([Cl^-] + [CO_2])$, is normal (6–15 mmol/L). In contrast, the other mechanisms, discussed below, are all associated with an increased anion gap attributable to abnormal accumulation of anions (inorganic or organic). These acids often are not measured directly. It is important to note that bicarbonate concentrations decrease naturally when another weak acid, such as lactic acid, is present in excess, because carbonic acid is formed and converted to carbon dioxide and water. The usual physiologic response to metabolic acidosis is an attempt to compensate by increasing ventilation and reducing P_{CO_2} , returning pH toward normal. When the P_{CO_2} is not reduced as much as expected, mixed acidosis is present and >1 underlying mechanism leading to acidosis should be considered.

Late metabolic acidosis of prematurity is an example of an increase in the hydrogen ion concentration attributable to intake in excess of renal clearance. In this situation, the ability of immature kidneys to excrete an acid load associated with a net-acid diet is exceeded. The urinary pH usually decreases below 5.5, and growth is impaired. This was more common when premature infant formulas were casein based but it still occurs, espe-

cially with intravenous alimentation. The anion gap is increased because of accumulating inorganic anions.¹⁸

The severe catabolic state of extremely ill neonates is an example of a condition that increases serum levels of inorganic acids (eg, phosphates and nitrates), which contribute to the metabolic acidosis seen in such infants. The most common mechanism for metabolic acidosis, however, is increased levels of organic acid, usually lactic acid, resulting from abnormal metabolism. Lactic acid levels in the circulation are increased when mitochondria are unable to convert lactate to carbon dioxide, water, and adenosine triphosphate. The mechanisms involve mitochondria that are not functioning properly (eg, Leigh disease or cyanide poisoning) or mitochondria that are deprived of oxygen. Common clinical conditions associated with oxygen deprivation at the tissue or cellular levels are hypoxemia, compromised cardiac output (cardiogenic, septic, or hypovolemic shock), severe anemia, carbon monoxide poisoning, and methemoglobinemia attributable to a genetic defect or exposure to a chemical or drug, such as inhaled nitric oxide.

These widely differing, underlying causes of metabolic acidosis require different approaches to treatment. If the problem is chronic loss of base and the acidosis is leading to secondary morbidities such as growth failure, then administration of base (such as acetate in the intravenous alimentation solution, sodium citrate, or dilute sodium bicarbonate) may be appropriate. Even under these circumstances, however, the efficacy and safety of sodium bicarbonate replacement therapy have not been proven. A trial comparing bicarbonate with acetate or placebo in infants with persistent metabolic acidosis attributable to chronic renal bicarbonate losses would be a welcome addition to the field of neonatology.

If the problem is poor perfusion, then addition of base will do little to correct the problem. Indeed, in the presence of poor perfusion, administration of base is likely to cause intracellular acidosis and venous hypercarbia. Successful treatment of metabolic acidosis, therefore, is highly dependent on proper identification and specific treatment of the underlying process. Once the process is known, a logical effective approach to therapy becomes possible. For example, in infants resuscitated successfully after severe perinatal distress, some degree of metabolic acidosis (lactic acidosis) persists for hours after birth. However, the underlying cause, hypoxia-asphyxia in the intrapartum period, has resolved. If blood pH were to be monitored serially, it very likely would increase spontaneously, eliminating the need for any buffer therapy. If the problem is poor cardiac output, then targeted measures to improve cardiac contractility and cardiac output might prove effective.

HISTORICAL RATIONALE FOR TREATING METABOLIC ACIDOSIS WITH SODIUM BICARBONATE

In the 1950s, it was noted that hypoglycemia, azotemia, hyperkalemia, and metabolic acidosis often developed in critically ill, premature infants before death. Because that era preceded the routine use of intravenous therapy, most preterm infants received no fluids and no source of dextrose. In 1963, Robert Usher¹⁹ published an

article describing early intravenous administration of glucose and sodium bicarbonate. This practice, which consisted of infusing a solution of 10% glucose in water, with 5 to 15 mEq/dL dilute sodium bicarbonate, at a rate of 65 mL/kg per day was widely adopted. Compared with historical control data, mortality rates for infants receiving the regimen described by Usher¹⁹ were remarkably reduced. Usher²⁰ published a follow-up article in 1967 in which he reported the results of administering as much sodium bicarbonate as necessary to correct the pH of neonates with respiratory distress syndrome. A hypertonic solution of 20 mEq/dL sodium bicarbonate in 10% dextrose was administered at a rate of 10 to 50 mL/kg over 3 hours. Compared with the results reported in 1963,¹⁹ mortality rates doubled, and increased intracranial hemorrhage was noted at autopsy.^{12,20} In 1972, Ostrea and Odell²¹ challenged the use of any sodium bicarbonate for infants with respiratory distress syndrome, pointing out that the chemical features of the intervention predict no benefit and highlighting the added danger of hypertonic infusions.

Although the regimen described by Usher¹⁹ represented a major advance at the time, the role of sodium bicarbonate per se in the infusion was not addressed systematically until 1977, when Corbet et al²² reported a RCT of bicarbonate in preterm infants. They compared sodium bicarbonate (30 infants) and no treatment (32 infants) and demonstrated that the addition of sodium bicarbonate to the intravenous infusion of newborns with acidemia was no more effective in decreasing morbidity (intracranial hemorrhage) and mortality rates than glucose and water alone.²² Furthermore, the pH was corrected just as quickly without sodium bicarbonate as with it. In the same year, Steichen and Kleinman²³ reported that, in puppies with hypercarbic acidosis and hypoxemia, sodium bicarbonate caused only a transient increase in pH, followed by a decrease, resulting in lower pH values than in the nontreated control animals. Furthermore, sodium bicarbonate caused a decrease in oxygenation, consistent with the alveolar air equation. Whether the sodium bicarbonate was given over 3 minutes or 3 hours, the hypoxemic acidemic animals given sodium bicarbonate fared worse than those given 5% dextrose in water alone. The animals with the best outcomes were those kept well oxygenated, which illustrates the importance of maintaining oxygen delivery to the tissues in the prevention and treatment of metabolic acidosis.^{12,23}

A 2005 Cochrane Systematic Review²⁴ attempted to evaluate the available evidence from RCTs of preterm infants with metabolic acidosis who were treated with infusion of base versus placebo or infusion of a fluid bolus. Only 2 small RCTs were found. The first was the aforementioned trial by Corbet et al.²² The second RCT compared sodium bicarbonate and albumin fluid bolus in 36 infants with metabolic acidosis.²⁵ The infants who received sodium bicarbonate had higher arterial blood pH values and lower base excess values 2 hours after the intervention. Other clinical outcomes were not reported. Neither trial assessed long-term neurodevelopmental outcomes. Appropriately, the authors of the Cochrane

review concluded that there was insufficient evidence to determine whether infusion of sodium bicarbonate or fluid bolus reduced morbidity and mortality rates in preterm infants with metabolic acidosis.²⁴ If there is not a single publication demonstrating that sodium bicarbonate is beneficial for infants with respiratory distress syndrome and a base deficit, why does it remain a component of clinical practice in many NICUs to treat such infants with sodium bicarbonate? This is a prime example of the double standard toward evidence-based medicine in neonatology. We hold new medications and interventions to a much higher standard for efficacy and safety than we do established but equally unproven therapies.

EVIDENCE FOR HARM

If there is no evidence that bicarbonate therapy is beneficial, is there any evidence that it can do harm? Indeed, there are clinical data that suggest that this drug should be used with caution, particularly in preterm infants. As early as 1967, Usher²⁰ showed that vigorous attempts to correct acidemia with large infusions of sodium bicarbonate were associated with increased mortality rates and increased intracranial hemorrhage in premature infants. Several other retrospective studies reported a strong relationship between intracranial hemorrhage and rapid infusions of hyperosmolar sodium bicarbonate.^{26,27} It was suggested that the rate and osmolality of the infusion were key factors and that the use of sodium bicarbonate should be limited to slow infusion of a dilute solution.²⁷ A recent study compared the effects of sodium bicarbonate, given as a rapid bolus versus a slow infusion over 30 minutes, on cerebral hemodynamics and oxygenation in preterm infants, using near-infrared spectrophotometry.²⁸ The authors found increases in cerebral blood volume in both cases, but the increase was more pronounced when sodium bicarbonate was administered rapidly. The deleterious effect of sodium bicarbonate infusion on intracellular pH also might contribute to negative outcomes.

There is accumulating evidence that sodium bicarbonate can have an adverse effect on systemic target organs, such as the heart, in young children beyond the neonatal period. Lipshultz et al²⁹ showed a direct relationship between serum bicarbonate levels and myocardial injury, as measured with serum cardiac troponin T levels. The authors questioned the value of bicarbonate use for patients with metabolic acidosis, noting the detrimental effects of bicarbonate with respect to hemodynamics, left ventricular function, intracellular pH, and oxygen delivery and consumption. In pediatric populations and in animal models, the possibility of worse clinical outcomes has been raised by several reports demonstrating that bicarbonate exacerbates cardiomyocyte injury and depresses cardiac function in patients with ongoing myocardial ischemia and/or acute renal failure.^{30–32} Neonates, who have been purported to have a high prevalence of myocardial injury,³³ may be particularly vulnerable to the use of a therapy that is associated with further myocardial injury.

CONCLUSIONS ON USE OF SODIUM BICARBONATE TO TREAT NEONATAL METABOLIC ACIDOSIS

Despite >50 years of experience with sodium bicarbonate, the data do not support a net beneficial effect of sodium bicarbonate in infants with metabolic acidosis. A reasonable but unproven exception is the replacement of base for ongoing renal or gastrointestinal losses. Possible 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, and deterioration of cardiac function. Lastly, it must be acknowledged that 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 are long overdue. In the meantime, clinicians should resist the common impulse to administer bicarbonate to infants with metabolic acidosis, recognizing the risks of immediate worsening of the intracellular milieu. Instead, they should concentrate their efforts on understanding and treating the underlying cause of the acidosis; *primum non nocere*.

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