

Role of Sodium Bicarbonate to Treat Neonatal Metabolic Acidosis: Beneficial or Not

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Summary:

Despite the lack of evidence for effectiveness of sodium bicarbonate in treatment of metabolic acidosis in critically ill patients who are admitted in neonatal and pediatric intensive care unit, bicarbonate administration is a common practice and has a long history of widespread use. The justification for persistent use of this controversial therapy comes from a variety of sources, many of them based in philosophy than in science. Clinicians must consider the intervention which will meet the therapeutic objective & existence of strong scientific evidence. To the contrary, there is increasing evidence of this

detrimental therapy and adverse effects include diminished oxygen delivery to tissues, worsening intracellular acidosis, aggravated myocardial injury, fluctuations in cerebral blood flow, intracranial hemorrhage and reduces the likelihood success of resuscitation. This review summarizes the evidence and examines the controversy over the use of bicarbonate to treat metabolic acidosis in neonate.

Key words: Sodium bicarbonate, Metabolic acidosis, Neonate, Clinical practice.

(J Bangladesh Coll Phys Surg 2017; 35: 80-85)

Introduction:

Over the past decades, since 1950s¹, neonatal clinical practice has included the use of sodium bicarbonate in the treatment of acute metabolic acidosis—specially, lactic acidosis—as a part of cardiopulmonary resuscitation of newborn.² The current edition of the Neonatal Resuscitation Program Guidelines continues to include sodium bicarbonate^{1,2} as a recommended secondary treatment for metabolic acidosis following the initial steps of resuscitation, which include adequate ventilation, cardiac compressions and volume expansion.² The 2008 update of Surviving Sepsis Guidelines suggests that ‘no evidence supports the use of bicarbonate therapy in the treatment of hypoperfusion-induced lactic acidosis associated with sepsis’ and recommend against the use of sodium bicarbonate in those patients with pH at least 7.15.^{3,4} This strong recommendation is based upon moderate quality evidence. Therefore, the use of sodium bicarbonate for treatment of severe metabolic acidosis continues to generate intense debate.^{3,5,6} Surprisingly, there are no large randomized controlled clinical trials for base recommendations.³ This article review the issue of

sodium bicarbonate in treatment of metabolic acidosis due to tissue hypoxia or poor tissue perfusion in neonate.

Cause of metabolic acidosis in neonate

Metabolic acidosis in neonate is a common finding in NICUs with a low pH in blood gas sample.⁷ Common clinical conditions associated with oxygen deprivation at tissue or cellular level due to hypoxemia and cardiopulmonary disorders are asphyxia neonatorum, sepsis, pneumonia, hyaline membrane disease, hypovolemia, hypothermia, anaemia³, low cardiac output and poor tissue perfusion, cardiac failure or congenital cardiac anomalies etc.⁸ Three common consequences are –a) loss of base from renal or GIT routes, b) intake of more acid than kidneys can excrete and c) abnormal metabolism resulting in increased endogenous acids (inorganic acids from rapid tissue catabolism and organic acids from anaerobic metabolism).⁷ Bicarbonate loss can be result of renal tubular acidosis or chronic diarrhea.^{9,10} Metabolic acidosis is diagnosed when the blood pH is below 7.30 with low bicarbonate concentration and a normal or low PCO₂.⁷

Mechanism of metabolic acidosis in neonate

Metabolic acidosis is an acid-base disturbance resulting from consumption or loss of buffers that decreases bicarbonate concentration in blood.² It is important to note that bicarbonate concentrations decrease naturally

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Received: 21 November 2016 **Accepted:** 5 March 2017

when another weak acid, such as lactic acid, is present in excess.^{7,11} Accumulation of lactic acid, a result of metabolism of carbohydrate in the absence of oxygen is a byproduct of glycolysis³ and refer to as hypoxic lactic acidosis.² As oxygen delivery and utilization are fundamental to normal metabolism of glucose, pyruvate and lactate, disruption of any part of oxygen transport can result in excess lactate production. Inadequate total body oxygen delivery is due to shock, whether hypovolemic, cardiogenic, distributive, obstructive or most commonly combination of these entities.³ Lactate clearance occurs due to metabolism of pyruvate in liver, more than 50% of clearance.^{12,13} Additionally, urinary excretion of lactate can rise to at least 10% (normally under 2%) with markedly elevated lactate levels.¹⁴ It appears that circulating inflammatory mediators which extract lactate from any organ produces excess lactate due to impaired hepatic clearance.^{3,15,16}

Reduced oxygen availability leads to acidosis in all body compartments and liberate lactic acid by anaerobic metabolism. Lactate accompanies metabolic acidosis, in turn, consumes blood buffer bases,^{7,11} mostly HCO_3^- in extracellular fluid. Lactic acidosis involves consumption, not loss of buffers.² Actually lactic acid is not the major source of H^+ and most of H^+ load derived from hydrolysis of adenosine triphosphate to adenosine diphosphate and inorganic phosphate. Thus, metabolic acidosis associated tissue hypoxia reduce the energy stores or energy charge and compensatory mechanisms are exhausted. The presence of metabolic acidosis as estimated by reduced blood buffer base or pH does not correlate well with measured levels of lactate.^{2,17,18,19,20} The usual physiologic response to metabolic acidosis attempts to compensate by increasing ventilation^{7,21} and reduce PCO_2 , returning pH towards normal. When the PCO_2 is not reduced as much as expected, mixed acidosis present.⁷

Evolution of intravenous administration of sodium bicarbonate for correcting metabolic acidosis in neonate

Sodium bicarbonate was first commercially produced in the late 1950s, used in premature infants before death to prevent hypoglycemia, azotemia, hyperkalemia and for correcting metabolic acidosis. In 1963, Robert Usher²² published an article describing early intravenous administration of glucose and sodium bicarbonate. This practice, which consisted of infusing a solution of 10%

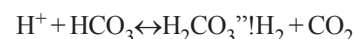
glucose in water, with 5 to 15 mEq/dl dilute sodium bicarbonate, at a rate of 65 ml/kg was widely adopted. Usher published²³ a follow-up article in 1967 in which he reported the results of administering as much sodium bicarbonate as necessary to correct the pH of neonates with respiratory distress syndrome. Treatment of metabolic acidemia with sodium bicarbonate remains a common practice in many pediatric intensive care units and operating rooms.²⁴

Effects of sodium bicarbonate administration

Administration of sodium bicarbonate causes an immediate and transient increase in the production of nonmetabolic CO_2 ,^{8,25,26} as well as a slight increase in plasma pH^{8,27} and serum osmolality.^{28,29} This increase in serum osmolality²⁹ leads to a flow of intracellular water into extracellular space to restore osmotic equilibrium and to an increase in arterial hemoglobin concentration and a decrease in hematocrit.^{26,28,29} This may play a role in pathogenesis of intracranial hemorrhage^{2,30} and effects on blood brain barrier³¹ via vasodilatation and decrease viscosity.³² In preterm infants, the use of sodium bicarbonate has been linked to hypernatremia and death.^{33,34,35} Additionally, sodium bicarbonate lowered plasma ionized calcium significantly.^{3,11} Bicarbonate exacerbates cardiomyocyte injury and depresses cardiac function in patients with ongoing myocardial ischemia and/or acute renal failure.^{36,37,38}

Biochemical basis of harm

Bicarbonate system can buffer an acid load effectively only when the lungs can remove excess carbon dioxide from the blood effectively.⁷ Infusing bicarbonate to buffer in lactic acidosis by reducing the excess H^+ and buffering H^+ increases CO_2 with increased ventilation requirements by shifting Henderson–Hasselbalch equation to the left.²



It follows that administration of sodium bicarbonate to a patient with inadequate minute ventilation would cause worsening acidosis, with CO_2 accumulation. The generated CO_2 diffuses rapidly across cell membranes to equilibrate between intracellular and extracellular compartments, leading to intracellular acidosis. So, bicarbonate lags in vascular space. The negative consequence causes an immediate decrease in

intracellular pH and impairment of cellular function.^{3,7,11,21} Due to these biochemical facts, many controlled clinical studies of bicarbonate administration have failed to show benefit and several have documented harm.⁷

Evidence based evaluation of the use of sodium bicarbonate in metabolic acidosis

The authors of 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.³⁹ At the same time that Usher's regimen was established, experiments on fetal lambs and fetal monkeys were said to demonstrate that an infusion of glucose and sodium bicarbonate prolonged survival after asphyxia and possibly reduced the degree of cerebral damage in experimental animals.⁴⁰ Also, Rudolph and Yuan, found that rapid correction of acidosis by the use of bicarbonate buffers could rapidly reverse the general hemodynamic effects resulting from pulmonary vasoconstriction associated with hypoxia.⁴¹ In truth, the early experimental data relating to correction of neonatal metabolic acidosis were neither extensive nor compelling and modern data do not support the continued use of sodium bicarbonate. In 1968, a controlled prospective trial in low birth weight newborn were unable to demonstrate any benefits in terms of improved oxygenation by reversal of right to left shunt following infusion of sodium bicarbonate.⁴² In 1972, Ostrea and Odell challenged the use of sodium bicarbonate for infants with respiratory distress syndrome and stated that the intervention predict no benefit and highlighting the added danger of hypertonic infusions.²⁵ In 1974, Odell called the use of sodium bicarbonate a "therapeutic misadventure in neonatal care".⁴³ Seigel *et al.* demonstrated an increased osmolality and decreased hematocrit in critically ill neonates following use of sodium bicarbonate in treatment of metabolic acidosis.²⁹

Sodium bicarbonate causes significant increases in partial pressure of arterial CO₂ in mechanically ventilated patients.⁴⁴ In 1977, Finberg cautioned against the use of hyperosmolar concentrations of sodium bicarbonate as a treatment for perinatal asphyxia. He noted the danger of a transient or unsteady state solute gradient of 5 to 6 mOsm for plasma water over brain extracellular

fluid, sufficient water flows out of brain to eliminate the gradient and results in cerebral shrinkage and hemorrhage.⁴⁵ Arterial blood gas do not reflect accurately what is occurring in tissues. Worsening of mixed venous acidosis has been shown to result when bicarbonate is given.⁴⁶ Since CO₂ diffuses into cell rapidly and the bicarbonate molecule does not, administration of this base may be counter product, adding to, rather than combating intracellular acidosis.²⁵ Indeed, Howell recently underscored the observation that sodium bicarbonate may not be helpful in hypoxic metabolic acidosis and may, in reality, be detrimental. In fact, in sick preterm neonate, sodium bicarbonate may create a situation that lowers intracellular pH.⁴⁷

In 1990, Cooper found that correction of acidemia using sodium bicarbonate does not improve hemodynamics in critically ill patients with metabolic acidosis and increased blood lactate or the cardiovascular response to infused catecholamines in these patients. Sodium bicarbonate decreases plasma ionized calcium and increases Pco₂.⁴⁸ Also, in absence of vasopressor agents, administration of hypertonic solutions, specially buffer solutions may adversely affect cardiac resuscitation efforts by reducing coronary perfusion pressure below critical threshold.⁴⁹ Mintzer shows that sodium bicarbonate infusion decreased base deficits and increased pH though produced no desirable effects or benefits on cardiopulmonary parameters including regional oxygen saturation and fractional tissue oxygen extraction in extremely premature neonates during the first week.⁵⁰ A recent study was conducted in resuscitation of hypoxic newborn piglets with severe acidosis, the administration of sodium bicarbonate improved the recovery of pH and HCO₃⁻ faster than those of hypoxia-reoxygenation controls, particularly during the first hour of regeneration. Despite faster recovery no effect on systemic and pulmonary hemodynamic changes when compared with hypoxia-reoxygenation controls.⁵¹

On the other hand, in presence of sodium bicarbonate, the peroxidase activity of superoxide dismutase can be enhanced dramatically^{52,53} and reduced cortical H₂O₂ accumulation. Similarly, increased DNA damage has been reported by addition of bicarbonate to superoxide dismutase- H₂O₂ system.⁵⁴

To date, there have been only two small prospective randomized studies examining the role of sodium

bicarbonate in lactic acidosis.^{48,55} These findings with respect to physiological changes were similar with sodium bicarbonate compared with physiologic saline treatment. Additionally, sodium bicarbonate lowered plasma ionized calcium significantly compared with physiologic saline. Despite the large difference in pH 15 mins following treatment, no difference was detected in cardiac output or mean arterial pressure. This was true even for patients with severe acidemia and pH less than 7.15.⁴⁸ The increase in pH was transient so that much of bicarbonate effect was gone after 30 mins.³ So, Boyd and Wally agreed with the recommendation of the 2008 Surviving Sepsis guidelines that sodium bicarbonate not be given at pH greater than 7.15. Indeed, they thought that bicarbonate administration is indicated for lactic acidosis due to shock for pH above 7.0. They recommended that sodium bicarbonate should be used as slow infusion and after a planning for clearing the produced CO₂ and measuring & correcting ionized calcium as the resultant 10% drop may decrease cardiac and vascular contractility which are due to response of catecholamines.³ Lipshultz *et al* showed a direct relationship between serum bicarbonate levels and myocardial injury with serum cardiac troponin T levels.⁵⁶ All reviews of use of bicarbonate in neonatal resuscitation¹ concluded that the treatment is more likely to lead to problems such as intracellular acidosis^{57,58,59} and hyperosmolality,⁶⁰ than to facilitate resuscitation. The guidelines from the American Heart Association manual on Neonatal Advanced Life Support no longer recommended bicarbonate in front line therapy, noting that there is no systemic evidence for its efficacy.⁶¹

Conclusions:

Sodium bicarbonate is commonly used medication administered for rapid correction of metabolic acidosis in neonatal intensive care. Despite >50 years of experience, basic science and observational studies do not support a net beneficial effect of sodium bicarbonate in neonate with metabolic acidosis. Additionally, it causes fluctuation in cerebral blood flow, intracranial hemorrhage, diminished oxygen delivery to tissues, worsening intracellular acidosis, aggravated myocardial injury and deterioration of cardiac function. It also acknowledged that current published recommendations for dose, dilution and rate of administration are largely arbitrary. According to these issues, the neonatologist should articulate specific therapeutic objectives and goal

to reduce acidosis in the microenvironment. The clinician should avoid unnecessary sodium bicarbonate infusion without justification.

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