REVIEW ARTICLE

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

M AFRIN

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 1950s[1], 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.

Address of Correspondence: Dr. Manifa Afrin, Registrar, NICU, MH Samorita Medical College and Hospital. Mobile: 01712089368, E-mail address- manifaafrin@gmail.com

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

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, anaemia[3], 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 PCO_2.[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

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 glycolysis[3] 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 Usher[22] 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 published[23] 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 academia 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 osmolality[29] 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 barrier[31] 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]

$$H^+ + HCO_3 \leftrightarrow H_2CO_3 \text{"!} H_2 + CO_2$$

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 CO_2 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 CO_2 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 academia 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 Pco_2.[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 thresold.[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 HCO_3^- 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 H_2O_2 accumulation. Similarly, increased DNA damage has been reported by addition of bicarbonate to superoxide dismutase- H_2O_2 system.[54]

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

bicarbonate in lactic acidosis.[48,55] There 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 academia 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 CO_2 and measuring & correcting ionized calcium as the resultant 10% drop may decrease cardiac and vascular contractility which are due to response ofcatecholamines.[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 resuscitation[1] 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.

References:

1. Hein HA: The use of sodium bicarbonate in neonatal resuscitation: help or harm? Pediatrics 1993; 91(2): 496-97.
2. Johnson PJ. Sodium bicarbonate use in the treatment of acute neonatal lactic acidosis: benefit or harm? Neonatal Netw 2011; 30:199-205. Doi: 10.1891/0730-0832.30.3.199
3. Boyd JH and Walley KR. Is there a role for sodium bicarbonate in treating lactic acidosis from shock? Current Opinion in critical care 2008; 14:379-83.
4. Dellinger RP, Levy MM, Carlet JM, *et al*. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock. Crit Care Med 2008; 36:296-327.
5. Gehlbach BK, Schmidt GA. Bench-to-bedside review: treating acid-base abnormalities in the intensive care unit: the role of buffers. Crit Care 2004; 8: 259-65.
6. Forsythe SM, Schmidt GA. Sodium bicarbonate for the treatment of lactic acidosis. Chest 2000; 117:260-67.
7. Aschner JL, Poland RL. Sodium bicarbonate: basically useless therapy. Pediatrics 2008; 122:831-35. Doi:10.1542/peds.2007-2400.
8. Laptook AR. The effect of sodium bicarbonate on brain blood flow and O_2 delivery during hypoxemia and academia in piglet. Pediatric Research 1985; 19(8):815-9.
9. Quigley R, Baum M. Neonatal acid base balance and disturbance. Seminar Perinatol 2004; 28(2):97-102.
10. Roth KS, Chan JCM. Renal tubular acidosis: a new look at an old problem. Clin Pediatr (Phila) 2001; 40(10): 533-43.
11. Ammari AN, Schulze KF. Uses and abuses of sodium bicarbonate in the neonatal intensive care unit. Curr Opin Pediatr 2002; 14:151-6.
12. Cohen RD. Disorders of lactic metabolism. Clin Endocrinol Metab 1976; 5:613-25.
13. Cohen RD, Iles RA. Lactic acidosis: some physiological and clinical considerations. Clin Sci Mol Med 1977;53:405-10.
14. Bellomo R. Bench to bedside review: lactate and the kidney. Crit Care 2002; 6:322-6.
15. Severin PN, U hing MR, Beno DW, Kimura RE. Endotoxin-induced hyperlactatemia results from decreased lactate clearance in hemodynamically stable rats. Crit Care Med 2002; 30:2509-14.
16. Chrusch C, Bands C, Bose D, *et al*. Impaired hepatic extraction and increased splanchic production contribute

to lactic acidosis in canine sepsis. Am J Respir Crit Care Med 2000:161:517-26.

17. Deshpande SA, Platt MP. Association between blood lactate and acid-base status and mortality in ventilated babies. Arch Dis Child Fetal Neonatal Ed 1997;76: F15-20.

18. Charpie JR, Dekeon MK, Goldberg CS, *et al.* Serial blood lactate measurements predict early outcome after neonatal repair or palliation for complex congenital heart disease. J Thorac Cardiovasc Surg 2000; 120:73-80.

19. Hatherill M, McIntyre AG, Wattie M, *et al.* Early hyperlactataemia in critically ill children. Intensive Care Med 2000; 26:314-8.

20. Cheung P, Finer N. Plasma lactate concentration as a predictor of death in neonates with severe hypoxemia requiring extracorporeal membrane oxygenation. J Pediatr 1994; 763-8.

21. Ho JJ. Sodium bicarbonate infusion during resuscitation of infants at birth: RHL commentary (last revised: 1 february2010). *The WHO Reproductive Health Library*; Geneva: World Health Organization.

22. Usher R. Reduction of mortality from respiratory distress syndrome of prematurity with early administration of intravenous glucose and sodium bicarbonate. Pediatrics 1963; 32(6): 966-75.

23. Usher R. Comparison of rapid versus gradual correction of acidosis in RDS of prematurity. Pediatr Res 1967; 3: 221.

24. Buckley EM, Naim MY, Lynch JM, Goff DA. *etal.* Sodium bicarbonate causes dose-dependent increases in cerebral blood flow in infants and children with single-ventricle physiology. Pediatr Res 2013; 73(5):668-73. Doi: 10.1038/pr.2013.25

25. Ostrea EM, Odell GB. The influence of bicarbonate administration on blood pH in a "closed system": clinical implications. J Pediatr 1972; 80(4):671-80.

26. Singer RB, Deering RC, Clark JK. The acute effects in man of a rapid intravenous infusion of hypertonic sodium bicarbonate solution. II. Changes in respiration and output of carbon dioxide. J Clin Invest 1956; 35:245-53.

27. Velden AAVA, Hopman JC, Klaessens JH, Feuth T, Sengers RC, Liem KD. Effects of rapid versus slow infusion of sodium bicarbonate on cerebral hemodynamics and oxygenation in preterm infants. Biol Neonate 2006; 90:122-7.

28. Kravath RE, Aharon AS, Abal G, Finberg L. Clinically significant physiologic changes from rapidly administered hypertonic solutions: acute osmol poisoning. Pediatrics 1970; 46: 266-75.

29. Seigel SR, Phelps DL, Leake RD, Oh W. The effects of rapid infusion of hypertonic sodium bicarbonate in infants with respiratory distress. Pediatrics 1973; 51: 651-4.

30. Finberg L, Luttrell C, Redd H. Pathogenesis of lesions in the nervous system in hypernatremic states. Pediatrics 1959; 23:46-53.

31. Rapoport SI, Hori M, Klatzo I. Testing of a hypothesis for osmotic opening of the blood-brain barrier. Am J Physiol 1972; 223:323-31.

32. Younkin DP, Reivich M, Jaggi JI, Obrist WD, Delivoria-Papadopoulos M. The effect of hematocrit and systolic blood pressure on cerebral blood flow in newborn infants. J Cereb Blood Flow Metab 1987; 7:295-9.

33. Berg CS, Barnette AR, Myers BJ, Shimony MK, Barton AW, Inder TE. Sodium bicarbonate administration and outcome in preterm infants. J Pediatr 2010; 157:684-7.

34. Papile LA, Burstein J, Burstein R, Koffler H, Koops B. Relationship of intravenous sodium bicarbonate infusions and cerebral intraventricular hemorrhage. J Pediatr 1978; 93:834-6.

35. Simmons MA, Adcock EW 3rd, Bard H, Battaglia FC. Hypernatremia and intracranial hemorrhage in neonates. N Engl Med 1974; 291:6-10.

36. Sirieix D, Delayance S, Paris M, Massonnet- Castel S, Carpentier A, Baron JF. Tris-hydroxymethane and sodium bicarbonate to buffer metabolic acidosis in an isolated heart model. Am J Respir Crit Care Med 1997; 155(3): 957-63.

37. Marangoni R, Civardi F, Masi F, *et al*. Lactate versus bicarbonate on-line hemofiltration: a comparative study. Artif Organs 1995; 19(6):490-5.

38. Wakabayashi Y, Ohwada T, Kikawada R. Haemo-dialysis/ filtration using sodium bicarbonate depresses cardiac function in critically ill patients with acute renal failure. Jpn Circ J 1994; 58(2):81-6.

39. Lawn CJ, Weir FJ, McGuire W. Base administration or fluid bolus for preventing morbidity and mortality in preterm infants with metabolic acidosis. Cochrane Database Syst Rev. 2005; 2(2):CD003215.

40. Dawes GS, Jacobson HN, Mott JC, Shelley HJ, Stafford A. The treatment of asphyxiated, mature fetal lambs and rhesus monkeys with intravenous glucose and sodium bicarbonate. J Physiol 1963; 169:167-85.

41. Rodolph AM, Yuan D. Response of the pulmonary vasculature to hypoxia and H ion concentration changes. J clin Invest. 1966; 45:399-411.

42. Sinclair JC, Engel K, Silverman W, *et al*. Early correction of hypoxemia and academia in infants of low birth weight: a controlled trial of oxygen breathing, rapid alkali infusion and assisted ventilation. Pediatrics 1968; 42:565-89.

43. Odell GB. Therapeutic misadventures in neonatal care. In: Gluck L, ed. Modern perinatal Medicine. Chicago, IL: Yearbook Medical publishers Inc; 1974; 323-7.

44. Levraut J, Garcia P, Glunti C, *et al*. The increase in CO_2 production induced by $NaHCO_3$ depends on blood albumin

and hemoglobin concentrations. Intensive Care Med 2000; 26:558-64.

45. Finberg L. The relationship of intravenous infusions and intracranial hemorrhage: a commentary. J Pediatr 1977; 91:777-8.

46. Weil MH, Trevino RP, Rackow EC. Sodium bicarbonate during CRP: does it help or hinder? Chest 1985; 88: 487

47. Howell JH. Sodium bicarbonate in the perinatal setting: revisited. Clin Perinatol 1987; 14: 807-16.

48. Cooper DJ, Walley KR, Wiggs BR, Russell JA. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis, A prospective, controlled study. Ann Intern Med 1990; 112: 492-8.

49. Kette F, Weil MH, Gazmuri RJ. Buffer solutions may compromise cardiac resuscitation by reducing coronary perfusion pressure. JAMA 1991; 266:2121-6.

50. Mintzer JP, Pervez B, Alpan G, lagamma EF. Effects of sodium bicarbonate correction of metabolic acidosis on regional tissue oxygenation in very low birth weight neonates. Journal of Perinatology 2015; 35:601-6.

51. Liu J-Q, Manouchehri N, Lee T-F, Yao M, Bigam DL, *et al.*Infusing sodium bicarbonate suppresses hydrogen peroxide accumulation and superoxide dismutase activity in hypoxic-reoxygenated newborn piglets. PLoS ONE 2012; 7(6):e39081. Doi:10.1371/journal.pone.0039081

52. Kalyanaraman B, Joseph J, Zhang H. Bicarbonate enhances nitration and oxidation reactions in biological systems-role of reactive oxygen and nitrogen species. Adv Exp Med Biol 2001; 500: 175-82.

53. Medinas DB, Cerchiaro G, Tfindade DF, Augusto O. The carbonate radical and related oxidants derived from bicarbonate buffer IUBMB Life 2007; 59: 255-62.

54. Barbosa LF, Garcia CC, Mascio PD, Medeiros MHD. DNA oxidation, strand-breaks and etheno-adducts formation promoted by Cu, Zn-superoxide dismutase-H_2O_2 in the presence and absence of bicarbonate. Dalton Trans 2009; 28: 1450-9.

55. Mathieu D, Neviere R, Billard V, *et al*. Effects of bicarbonate therapy on hemodynamics and tissue oxygenation in patients with lactic acidosis: a prospective, controlled clinical study. Crit Care Med 1991; 19: 1352-6.

56. Lipshultz Se, Somers MJ, Lipsitz SR, Colan SD, Jabs K, Rifai N. Sreum cardiac troponin and subclinical cardiac status in pediatric chronic renal failure. Pediatrics 2003; 112(1): 79-86.

57. Levraut J, Ginuti C, Ciebiera J- P, *et al*. Initial effect of sodium bicarbonate on intracellular pH depends on the extracellular nonbicarbonate buffering capacity. Crit Care Med 2001; 29:1033-9.

58. Goldsmith DJ, Forni LG, Hilton PJ. Bicarbonate therapy and intracellular acidosis. Clin Sci (Colch) 1997; 93:593-8.

59. Wyckoff MH, Periman J, Niermeyer S. Medications during resuscitation: what is the evidence? Semin Neonatol 2001; 6:251-9.

60. Lou HC, Lassen NA, Fris-hansen B. Decrease cerebral blood flow after administration of sodium bicarbonate in distressed newborn infant. Acta Neorol Scand 1978; 57:239-47.

61. Niemeyer S. Kattwinkel J. Reempts PV, *et al*. International guidelines for neonatal resuscitation: an excerpt from the Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: International Consensus on Science. Contributors and Reviewers for the Neonatal Resuscitation Guidelines. Pediatrics 2000; 106. http://www.pediatrics.org/cgi/reprint/106/3/e29