



Annals of Pediatrics and Child Care

Research Article

Francois B, et al. Ann Pediatr Child Care: APCC-100005.

Sodium Bicarbonate Administration and Metabolic Acidosis of Preterm Infants: A Useless Therapy?

Bérenère FRANCOIS^{1*}, Coralie LO PRESTI², Sophie HASSID¹, Renaud VIALET¹ and Claire NICAISE¹

¹Service de réanimation pédiatrique et néonatale, Hôpital Nord, Marseille, France

²Pharmacie centrale, Hôpital Nord, AP-HM, chemin des Bourrely, France

*Corresponding author: Bérenère FRANCOIS, Service de réanimation pédiatrique et néonatale, Hôpital Nord, AP-HM, chemin des Bourrely, 13015 Marseille, France.

Citation: Francois B, Presti CL, Hassid S, Vialet R, Nicaise C (2019) Sodium Bicarbonate Administration and Metabolic Acidosis of Preterm Infants: A Useless Therapy?. Ann Pediatr Child Care: APCC-100005.

Received Date: 20 March, 2019; **Accepted Date:** 25 April, 2019; **Published Date:** 07 May, 2019

Abstract

Background: Metabolic acidosis due to renal loss is a common complication of prematurity. Sodium bicarbonate is still frequently used in this indication despite the lack of recommendation. The objective was to evaluate the restriction of the indication of sodium bicarbonate therapy in metabolic acidosis due to renal immaturity in preterm infants in two historical series of patients. In addition, we measured the effect of this therapy on acid-base status.

Methods: This was a retrospective monocentric study from two historical cohorts. All preterm infants under 28 weeks of gestation with metabolic acidosis ($\text{pH} < 7.20$ and excess base (EB) ≤ -10 mmol / L) were included. During the first period (June 2011 to May 2012) patients were treated with sodium bicarbonate if the EB was ≤ -10 mmol / L. In the second period (October 2012 to September 2013), patients were treated if EB ≤ -13 mmol /L.

Results: Twenty-seven patients were included during the first period with an average gestational age of 26.5 weeks versus 38 patients during the second period with an average gestational age of 26.1 weeks ($p = 0.41$). In period 1, 27/27 patients (100%) were treated against 21/38 (55.2%) during the second period ($p < 0.001$). There was no significant difference over the two periods regarding the difference in pH, pCO₂ and EB between the end and the beginning of sodium bicarbonate treatment.

Conclusions: Changing our protocol decreased sodium bicarbonate use and was not associated with any change in pH, pCO₂ and EB.

Keywords: Metabolic acidosis; Preterm infants; Sodium bicarbonate

Introduction

Metabolic acidosis with loss of bases is a common complication of prematurity. It is mainly due to renal immaturity [1]. Full performance of renal functions depends on gestational age and postnatal age, so that glomerular and tubular functions are immature [2,3]. Tubulopathy of preterm is responsible for excessive loss of bicarbonate due to a lack of tubular reabsorption of bicarbonate, electrolytes and small proteins that lead to metabolic

acidosis, fluid, electrolyte disturbances, and weight problems [2,4,5]. Metabolic acidosis may have serious consequences: impaired cardiovascular function, cardiac arrhythmia, inflammation and decreased immune response [6]. Metabolic acidosis in prematurity has been associated with the development of intraventricular hemorrhage, periventricular leukomalacia and delayed psychomotor development [1]. For more than 60 years, sodium bicarbonate administration has been used in case of metabolic acidosis management in order to normalize the pH by acid-base reaction [7-10]. There are no recommendations in the treatment of metabolic acidosis of premature renal failure, although

Citation: Francois B, Presti CL, Hassid S, Vialet R, Nicaise C (2019) Sodium Bicarbonate Administration and Metabolic Acidosis of Preterm Infants: A Useless Therapy?. Ann Pediatr Child Care: APCC-100005.

this treatment is widely used. Several authors, however, have described occasional severe complications such as intraventricular hemorrhage (IVH) following the use of bolus bicarbonate infusion in preterm newborns [1,11].

The main objective of our study was to evaluate the restriction of the indication of sodium bicarbonate in metabolic acidosis due to renal immaturity in preterm under 28 weeks of gestation during two periods and to assess the outcome of untreated patients during the second period.

The secondary objective was to evaluate the consequences of this change of practice on acid-base status.

Materials and Methods

Patients and methods: This is a retrospective monocentric study in the neonatal intensive care unit of the Hôpital Nord of Marseille (France) from two historical cohorts. All preterm infants under 28 weeks of gestation with metabolic acidosis were included. Metabolic acidosis was defined as pH less than 7.20 and EB less than or equal to -10 mmol / L. During the first period, from June 2011 to May 2012, patients were treated with continuous sodium bicarbonate infusion at 1 to 2 mEq / kg / day if the EB was less than or equal to -10 mmol / L, until correction of metabolic acidosis. During the second period, from October 2012 to September 2013, patients were treated if the EB was less than or equal to -13 mmol / L. The factors taken into account were: gestational age, birth weight, age at the time of treatment, pH, pCO₂ and EB (before, during and at the end of sodium bicarbonate treatment), duration of treatment, the total dose administered, the occurrence of intraventricular hemorrhage stage III and / or IV according to the classification of Papile [12].

Primary outcome was the evolution of pH, pCO₂ (mmHg) and EB (mmol/l). Secondary outcome were the occurrence of IVH

III and IV and duration of treatment. The first day (D 0) considered is the first day of treatment ie when the EB was less than or equal to - 10 mmol / L in the “first period” group and less than or equal to -13 mmol / l in the “second period” group. End day was the last day of treatment. For untreated patients, the D0 was when the patient had an EB less than or equal to -10 mmol / L and the end day was 3 days later.

Statistical analysis: The differences between the end of treatment and the day 0 were calculated, mismatched differences between the values were observed between the end and the beginning of treatment for pH, PCO₂ and EB. For untreated patients in the «second period», the difference between first and third day was calculated. The comparisons between the quantitative variables were made by Student's t-test, and by the χ^2 test with a risk α fixed at 5%. The software used was PASW Statistics (V 17.0.2). The number of patients required was 32 patients (16 per group) as calculated with BioStat TGV (<http://marne.u707.jussieu.fr/biostatgv/>), with risk alpha 0.05 and beta 80%.

Ethics: The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and regional) and with the Helsinki Declaration of 1964, as revised in 2013.

Results

Twenty-seven patients were included during the first period with an average gestational age of 26.5 (**SD 2.5**) weeks versus 38 patients during the second period with an average gestational age of 26.1 (**SD 1.1**) weeks ($p = 0.41$). The mean birth weight was 0.96 kg (standard deviation: 0.45) in the first period versus 0.90 kg (standard deviation: 0.17) in the second period ($p = 0.57$). The main results are summarized in (Table 1).

	Period 1 (treatment threshold for EB ^s ≤ - 10 mmol/L)	Period 2 (treatment threshold for EB ^s ≤ - 13 mmol/L)	
Number of patients	27	38	$p < 0.001$
Number of treated patients (n [^] (%))	27 (100%)	21 (55.2%)	$p < 0.001$
Age at D0* of treatment(SD**) days	5.17 (1.5)	8.41 (4.07)	$p < 0.001$
Duration of treatment H ² (SD**)	119 (72)	89 (57)	$p=0,90$
Duration of metabolic acidosis	2.04 (1.19)	2.87 (1.63)	$p = 0.027$
Cumulated dose grams (SD**)	0.6 (0.4)	0.3 (0.3)	$p=0.004$
pH D0* (SD**)	7.19 (0.1)	7.14 (0.1)	NS

pH End [#] – pH D0 [*] (SD ^{**})	-0.01 (0.15)	0.02 (0.19)	p=0.40
pCO ₂ D0 [*] mmHg (SD ^{**})	44.7 (9.6)	47.9 (14.8)	NS
pCO ₂ End [#] – pCO ₂ D0 [*] mmHg (SD ^{**})	9 (15)	2 (17)	p=0.10
EB[§]D0[*](SD^{**})	-11.9 (2)	-12.9 (2.7)	NS
EB [§] End [#] – EB [§] D0 [*] (SD ^{**})	3.5 (4.5)	3.3 (4.8)	p=0.85
Intraventricular hemorrhage III and IV (n [^] (%))	3 (11.1%)	9 (23.7%)	p=0.198
Mean and standard deviation			
*D0 : 1st day of treatment, #End : end of treatment or at 3 days of evolution, §EB : excess base, †H : hours, ^n = number, **SD = standard deviation			

Table 1: Results of all patients

In period 1, 27/27 patients (100%) were treated against 21/38 (55.2%) during the second period (p <0.001). There was no significant difference over the two periods regarding the difference in pH, pCO₂ and EB between the end and the beginning of sodium bicarbonate treatment. In both periods, there were no cases of grade III IVH and the number of IVH cases was comparable between the two periods (p = 0.198).

If we restrict comparison between patients with an EB between -10 and -13 mmol/ L (Table 2): no patients in period 2 were treated. There was no difference in pH, pCO₂ and EB between the end and the beginning of sodium bicarbonate treatment. The modification of the protocol did restrict the sodium bicarbonate administration in our unit: 67 days of prescription in 2015 versus 394 days in 2012.

	Period 1 (treatment threshold for EB [§] ≤ - 10 mmol/L)	Period 2 (treatment threshold for EB [§] ≤ - 13 mmol/L)	
Number of patients	16	17	
Patients treated (n [‡] (%))	16 (100%)	0%	
pH End [#] – pH D0 [*]	-0.02 (0.13)	-0.04 (0.12)	p=0.61
pCO ₂ End [#] – pCO ₂ D0 [*] (mmHg)	12 (15)	8 (16)	p=0.49
EB [§] End [#] – EB [§] D0 [*]	2.7 (3.35)	0.5 (4.3)	p=0.12
Mean and standard deviation			
*D0 = 1st day when EB < - 10 mmol/L, # End = end of treatment or at 3 days of evolution, §EB : base excess, ‡ n = number.			

Table 2: Patients with EB between – 10 et -13 mmol/L

Discussion

Sodium bicarbonate treatment is very commonly used to treat metabolic acidosis in preterm infants, although there are no recommendations. Limited data had been published about this subject. The Cochrane review of 2010 found only two randomized controlled trials and one unpublished pilot study that were eligible for their criteria [1]. In our study, the protocol change did not show a significant difference on acid-base status between the treated and untreated group for an EB between -10 and -13 mmol/L. We did not find a beneficial effect of sodium bicarbonate treatment on the evolution of pH, pCO₂ and EB. Untreated patients did not present more complication or deeper acidosis. Several authors

have demonstrated that treatment with sodium bicarbonate in the metabolic acidosis of preterm has no effect on mortality and that it does not improve either the pH nor the psychomotor development [1,11,13-15]. Radde et al and Schwartz et al found no improvement in weight gain in these patients [16,17]. In addition, the renal immaturity responsible for this acidosis gradually corrects with age [2]. Saint-Faust et al estimated that nephrogenesis is complete between 34 and 36 GA [4]. Furthermore, treatment with sodium bicarbonate has been associated with intraventricular hemorrhage when delivered as a bolus [1,11,18]. The link between sodium bicarbonate infusion and intraventricular hemorrhage has not been established [10,15,19]. In our study we found no significant difference in the occurrence of intraventricular hemorrhage

between the two groups. However, this study was not designed to test this specific issue and is of insufficient power to exclude this side effect. Several authors have shown that rapid sodium bicarbonate infusion modifies the cerebral perfusion rate with a risk of cerebral complications, that the effect depends on the speed of injection and that there is a dose-dependent effect [1,10,18,20]. Van-Alfen et al advocate slow infusion of sodium bicarbonate to minimize alteration of brain flow [20]. This treatment has even been associated with an increase in mortality [11]. Lawn *et al*, emphasize that any addition of intravenous treatment in the preterm must be carefully considered [1]. Sodium bicarbonate therapy has known side effects. It may be responsible for hypernatremia, hypercapnia, hypokalemia, hypocalcemia, hyper-osmolarity, hemodynamic changes, and QT elongation [1,14,18,20,21]. Infusion of sodium bicarbonate precipitates with many compounds and often must be administered alone which may require additional peripheral venous route for the duration of treatment and can be responsible for local complication.

The limitations of our study were a limited number of patients and a study done at two periods with the risk of change of practice causing bias, we did not evaluate the consequence on growth.

No beneficial effects of bicarbonate therapy have been demonstrated so far but there is evidence of possible adverse effects. Changing our protocol decreased sodium bicarbonate use and was not associated with any change in acid-base status. Our data did not demonstrate any benefit from bicarbonate infusion in preterm infants.

References

- Lawn CJ, Weir FJ, McGuire W (2005) Base administration or fluid bolus for preventing morbidity and mortality in preterm infants with metabolic acidosis. *Cochrane Database Syst Rev* [Internet].
- Stritzke A, Thomas S, Amin H, Fusch C, Lodha A (2017) Renal consequences of preterm birth. *Mol Cell Pediatr* 4: 2.
- Gubhaju L, Sutherland MR, Horne RSC, Medhurst A, Kent AL, et al. (2014) Assessment of renal functional maturation and injury in preterm neonates during the first month of life. *Am J Physiol-Ren Physiol* 307: F149-158.
- Saint-Faust M, Boubred F, Simeoni U (2014) Renal Development and Neonatal Adaptation. *Amer J Perinatol* 31: 773-780.
- Ramiro-Tolentino SB, Markarian K, Kleinman LI (1996) Renal Bicarbonate Excretion in Extremely Low Birth Weight Infants. *Pediatrics* 98: 256.
- Kraut JA, Madias NE (2012) Treatment of acute metabolic acidosis: a pathophysiologic approach. *Nat Rev Nephrol* 8: 589.
- Alexander Aiken CG (2013) History of Medical Understanding and Misunderstanding of Acid Base Balance. *J Clin Diagn Res* [Internet].
- Aschner JL, Poland RL (2008) Sodium Bicarbonate: Basically Useless Therapy. *Pediatrics* 122: 831.
- Kalhoff H, Diekmann L, Kunz C, Stock GJ, Manz F (2008) Alkali therapy versus sodium chloride supplement in low birthweight infants with incipient late metabolic acidosis. *Acta Paediatr* 86: 96-101.
- Buckley EM, Naim MY, Lynch JM, Goff DA, Schwab PJ, et al. (2013) Sodium bicarbonate causes dose-dependent increases in cerebral blood flow in infants and children with single-ventricle physiology. *Pediatr Res*. 73: 668.
- Berg CS, Barnette AR, Myers BJ, Shimony MK, Barton AW (2010) Sodium Bicarbonate Administration and Outcome in Preterm Infants. *J Pediatr*. 157: 684-687.
- Papile L-A, Burstein J, Burstein R, Koffler H (1978) Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birth weights less than 1,500 gm. *J Pediatr* 92: 529-534.
- Bourchier D (2011) Bicarbonate therapy for infants. *J Pediatr* 158: 518.
- Adeva-Andany MM, Fernández-Fernández C, Mouriño-Bayolo D, Castro-Quintela E, Domínguez-Montero A (2014) Sodium Bicarbonate Therapy in Patients with Metabolic Acidosis. *Sci World J* 2014: 1-13.
- Behrman AJ, Adams JM, Kenny JD, Kennedy J, Rudolph AJ (1977) Controlled trial of bicarbonate therapy in high-risk premature newborn infants. *J Pediatr* 91: 771-776.
- Radde IC, Chance GW, Bailey K, O'Brien J, Day GM (1975) Growth and Mineral Metabolism in Very Low Birth Weight Infants. I. Comparison of the Effects of Two Modes of NaHCO₃ Treatment of Late Metabolic Acidosis. *Pediatr Res* 9: 564.
- Schwartz GJ, Haycock GB, Chir B, Edelmann CM Jr, Spitzer A (1979) Late metabolic acidosis: A reassessment of the definition. *J Pediatr* 95: 102-107.
- Collins A, Sahni R (2017) Uses and misuses of sodium bicarbonate in the neonatal intensive care unit. *USE MISUSE DRUGS Perinatol Neonatol* 22: 336-341.
- García-Pasquel MJ, Iglesias-Leboreiro J, Bernardez-Zapata I (2015) Correlation between the use of sodium bicarbonate and intraventricular hemorrhage in preterms. *Rev Médica Inst Mex Seguro Soc* 53: 512-517.
- van Alfen-van der Velden AAEM, Hopman JCW, Klaessens JHGM, Feuth T, Sengers RCA, et al. (2006) Effects of Rapid versus Slow Infusion of Sodium Bicarbonate on Cerebral Hemodynamics and Oxygenation in Preterm Infants. *Neonatology* 90: 122-127.
- Fanconi S, Burger R, Ghelfi D, Uehlinger J, Arbenz U (1993) Hemodynamic effects of sodium bicarbonate in critically ill neonates. *Intensive Care Med* 19: 65-69.