JPPT | Single-Center Retrospective Study

Incidence of Intracranial Hemorrhage in Patients Younger Than 2 Months Receiving Sodium Bicarbonate 4.2% vs 8.4%

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OBJECTIVE To assess the incidence of intracranial hemorrhage (ICH), including intraventricular hemorrhage, in infants receiving 4.2% or 8.4% sodium bicarbonate.

METHODS This is a single-center retrospective chart review of neonates and infants with a gestational age (GA) >32 weeks and a postnatal age <2 months who received sodium bicarbonate in an intensive care unit at an academic tertiary children's hospital. The primary outcome was the incidence of ICH in patients with baseline and follow-up head imaging. The secondary outcome was the incidence of ICH on follow-up head imaging, with or without baseline head imaging.

RESULTS There were 351 patients screened, with 135 meeting inclusion criteria. Of these, 84% were born ≥37 weeks GA. Forty-two met the criteria for the primary outcome. Study participants were further subdivided into 3 groups based on the concentration of sodium bicarbonate received: only 4.2%, only 8.4%, or a mixed group that received at least 1 dose each of 4.2% and 8.4%. Intracranial hemorrhage was noted in 1 patient in each group: 8.3%, 5.6%, and 8.3%, respectively (p = 1.00). For the secondary outcome, 11 ICHs were seen on head imaging: 11.3%, 3.8%, and 10%, respectively. There was no statistically significant difference in the incidence of ICH (p = 0.325).

CONCLUSIONS The incidence of ICH in term neonates and infants was not significantly different in those receiving 4.2% vs 8.4% sodium bicarbonate. Although additional studies are needed, this study suggests it may be possible to safely expand the use of 8.4% in neonates/infants ≥37 weeks GA. These results should not be applied to preterm neonates (<37 weeks GA and/or <1500 g) or neonates with additional ICH risk factors.

ABBREVIATIONS CCVCU, congenital cardiovascular care unit; GA, gestational age; ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage; NICU, neonatal intensive care unit

KEYWORDS intracranial hemorrhage; intraventricular hemorrhage; sodium bicarbonate

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Introduction

The routine use of sodium bicarbonate in cardiopulmonary resuscitation is not supported by the 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care.[1] This is because of observational data demonstrating an association with worse survival outcomes and adverse effects related to administration.[2] However, sodium bicarbonate may be considered for the treatment of metabolic acidosis, hyperkalemia, or prolonged cardiac arrest after effective ventilation, epinephrine, and chest compressions are provided.

There are 2 primary concentrations of sodium bicarbonate, with unclear guidance on when to use the 4.2% "infant" formulation vs the standard 8.4% formulation. The manufacturer's package insert suggests 4.2% is preferred for patients younger than 2 years to facilitate slow administration and decrease the risk of hypernatremia, decrease cerebrospinal fluid pressure, and decrease the risk of intracranial hemorrhage (ICH).[3] The American Academy of Pediatrics has 2 recommendations based on age and indication: 4.2% for patients younger than 2 years when used for cardiac arrest and 4.2% for patients younger than 28 days when used for metabolic emergency.[4]

Although the mechanism as to how sodium bicarbonate causes ICH is unclear, potential contributing factors include the rate of administration, the hyperosmolarity of concentrated sodium bicarbonate, hypernatremia from the sodium load, and the carbon

dioxide–generating properties of bicarbonate.[5–10] These factors are thought to lead to fluid shifts and subsequent changes in cerebral blood flow, thereby increasing the risk of ICH. No studies have directly assessed the impact of concentration on the incidence of ICH. Despite this, many organizations recommend slow administration of dilute sodium bicarbonate in children.[2–4]

There are varying practices regarding use of sodium bicarbonate 4.2% vs 8.4% in children's hospitals. A multicenter survey trial in Italy revealed inconsistent practices, including 4.2% formulation in all patients <5 kg, all patients <10 kg, or restricted to neonatal intensive care unit (NICU) patients only.[11] The purpose of this study was to assess the incidence of ICH in neonates and infants receiving sodium bicarbonate 4.2% vs 8.4% formulation, given the varying practices.

Materials and Methods

Study Design and Setting. This was a single-center retrospective chart review from January 1, 2013, to September 1, 2020. All neonates (≥32 weeks gestational age [GA]) and infants 2 months or younger who were admitted to an intensive care unit at an academic tertiary children's hospital and received intravenous sodium bicarbonate (4.2% or 8.4%) were screened. They were included if at least 1 head image after sodium bicarbonate administration was performed. Patients were excluded if they weighed less than 1500 g, had an ICH (including intraventricular hemorrhage [IVH]) on head imaging prior to sodium bicarbonate administration, had risk factors for an ICH prior to head imaging (extracorporeal membrane oxygenation, hypertensive urgency/emergency, transferred from an outside hospital after cardiac arrest), or if head imaging was more than 30 days after the last dose of sodium bicarbonate. Of note, a duration of 30 days was chosen in an attempt to capture events most likely due to sodium bicarbonate administration rather than other confounding events. Study participants were divided into 3 groups based on the concentration of sodium bicarbonate received: exclusively 4.2% formulation, exclusively 8.4% formulation, or a mixed group having received at least 1 dose of 4.2% and 1 of 8.4%. At our institution, the 4.2% formulation is typically used in the NICU exclusively, whereas other units use either 4.2% or 8.4%, at the discretion of the attending provider.

Outcome Measures. Patients' demographics, laboratory data (serum sodium concentrations within 24 hours of sodium bicarbonate administration, coagulation labs [platelets, international normalized ratio within 24 hours of head imaging], pH, and lactate), radiographic data, and details of IV bicarbonate treatment course (dose, frequency, and duration) were collected based on the retrospective review of electronic health records in EPIC. Our primary objective was the incidence of ICH, as documented by head imaging after bicarbonate administration and compared to a baseline head imaging. If there were several head images completed prior to sodium bicarbonate administration, the head image closest to the administration was data collected. Our secondary objective was the incidence of ICH, as documented by head imaging after bicarbonate administration, with or without a baseline head imaging.

Statistical Analysis. Descriptive statistics were performed on each variable in the data set. Chi-squared or Fischer exact (if counts <5) tests were performed on categoric variables. Data were checked for normality using Shapiro-Wilk test, with p value >0.05 as level of significance. One-way analysis of variance was used to analyze parametric variables, and the Kruskal-Wallis test was used for nonparametric variables. All statistical analyses were performed using IBM SPSS Statistics (version 25.0, IBM Corp, Armonk, NY). There is no published literature on effect size between 4.2% and 8.4% sodium bicarbonate. Assuming an α of 0.05 and 80% power and a conservative predicted effect size of 10%, a total of 200 patients in each group are needed. Assuming an α of 0.05 and 80% power and a more generous effect size of 50%, a total of 20 patients in each group are needed.[6]

Results

There were 351 patients screened for inclusion, with 135 patients included in the final analysis. The most common reason for exclusion was lack of head imaging after sodium bicarbonate administration (n = 115; 32.8%; see the Supplemental Figure). The median GA of the study participants was 39 + 0 weeks (IQR, 37 + 4 – 39 + 4) and median weight was 3.07 kg (IQR, 2.7–3.56). Patients received either the 4.2% formulation exclusively (n = 62), the 8.4% formulation exclusively (n = 53), or a combination of both (n = 20). Baseline demographics were similar among the 3 groups except for admitting unit, surgical history, and mechanical ventilation (Table 1). There was no difference in baseline demographics between those with ICH vs those without ICH.

Patients admitted to the NICU were more likely to receive the 4.2% formulation vs the 8.4% formulation (p = 0.001). Patients admitted to the congenital cardiovascular care unit (CCVCU) and those with a history of cardiac surgery were more likely to receive the 8.4% formulation vs the 4.2% formulation (p = 0.001). Mechanical ventilation prior to sodium bicarbonate administration was also statistically different, with 64.5% in the 4.2% group, 71.7% in the 8.4% group, and 95% in the mixed group (p = 0.032).

Sodium bicarbonate characteristics and confounding variables are recorded in Table 2. The most common indication for sodium bicarbonate was severe metabolic acidosis (>90% in each group), with the remainder receiving it for cardiac arrest. When given for metabolic acidosis, there was a statistically significant difference between the 3 groups in terms of pH and lactate

Table 1. Baseline Patient Characteristics

	Only 4.2% (n = 62)	Only 8.4% (n = 53)	Mixed Group (Both 4.2% and 8.4%) (n = 20)	p value
Gestational age, median (IQR), week + days	38 + 5 (37 + 1 – 39 + 4)	39 + 0 (37 + 6 – 39 + 6)	38 + 5 (36 + 3 – 39 + 2)	0.412
Male, n (%)	40 (64.5)	28 (52.8)	14 (70)	0.292
Birth weight, median (IQR), g	3120 (2680–3485)	3115 (2740–3585)	2985 (2630–3645)	0.561
In-house delivery, n (%)	47 (75.8)	29 (54.7)	13 (65)	0.343
Admitting unit, n (%)				
CCVCU	22 (35.5)	48 (90.6)	17 (85)	0.001*
NICU	38 (61.3)	4 (7.5)	2 (10)	0.001*
PICU	2 (3.2)	1 (1.9)	1 (5)	1.00
Surgical history, n (%)				
Cardiac surgery	32 (51.6)	40 (75.5)	16 (80)	0.009*
Other	3 (4.8)	1 (1.9)	0 (0)	1.00
Mechanical ventilation, n (%)	40 (64.5)	38 (71.7)	19 (95)	0.032*
Birth history, n (%)				
Cesarean	36 (58.1)	27 (50.9)	9 (45)	0.541
NSVD	26 (41.9)	26 (49.1)	11 (55)	0.541
APGAR scores, median (IQR)				
At 1 min	8 (6.25–8)	8 (7–9)	8 (5–8)	0.153
At 5 min	8 (8–9)	9 (8–9)	8 (8–9)	0.118
Additional scores	7 (7–8)	7 (7–7)	7 (6–7)	0.460
Resuscitation in the delivery room, n (%)	3 (4.8)	0 (0)	0 (0)	1.00
Compression time, median (IQR), min	1 (0.5–1)	0 (0)	0 (0)	1.00

APGAR, Appearance, Pulse, Grimace, Activity, Respiration; CCVCU, congenital cardiovascular care unit; NICU, neonatal intensive care unit; NSVD, normal spontaneous vaginal delivery; PICU, pediatric intensive care unit

* Statistically significant.

(p = 0.036 and 0.049, respectively). Additionally, age at time of the first dose was significantly different between the 3 groups, with a median age (in days) of 0.64 in the 4.2% group, 0.92 in the 8.4% group, and 1.32 in the mixed group (p = 0.013). The mixed group received significantly more doses and a larger cumulative sodium bicarbonate dose compared with the 4.2% and 8.4% groups (p = 0.001). The median time from last dose of sodium bicarbonate to head imaging was 15.8 hours. Serum sodium was assessed before sodium bicarbonate supplementation. There were 8 patients with hypernatremia (serum sodium >145 mEq/L) at baseline (range, 146–158), only 1 of whom was in the ICH group. This latter patient had a serum sodium concentration of 150 mEq/L before and 148 mEq/L after bicarbonate administration.

There were 42 patients who met the criteria for the primary outcome (had a baseline head imaging prior to sodium bicarbonate administration; Table 3). From the 42 patients, there were 3 ICHs noted, with 1 in each group (p = 1.00). As for the secondary outcome, there were 135 patients included, with 11 ICHs seen on follow-up head imaging. Of these 11 ICHs, 7 (11.3%) occurred in the 4.2% group, 2 (3.8%) in the 8.4% group, and 2 (10%) in the mixed group. The difference in the incidence of ICH was not found to be statistically significant between the sodium bicarbonate concentrations (p = 0.325). In the 4.2% group, 4 of these ICHs were grade I IVH, 1 was grade IV IVH, 1 was epidural, and 1 was subdural hemorrhage. In the 8.4% group, there was 1 grade I IVH and 1 subdural hemorrhage noted. Within the mixed group there was 1 grade I IVH and 1 intraparenchymal hemorrhage.

Discussion

Sodium bicarbonate recommendations remain controversial, given the lack of evidence comparing the dilute 4.2% to the 8.4% concentration. Our study found no statistical difference in the incidence of ICH in patients receiving 4.2% vs 8.4% sodium bicarbonate. Although patients greater than 32 weeks' gestation were included in this study, our population consisted primarily of term neonates and infants.

Table 2. Characteristics and Confounding Variables of Patients Receiving Intravenous Sodium Bicarbonate

	Only 4.2% (n = 62)	Only 8.4% (n = 53)	Mixed group (Both 4.2% and 8.4%) (n = 20)	p value
Indication, n (%)				
Cardiac arrest	2 (3.2)	1 (1.9)	1 (5)	0.774
Metabolic acidosis	60 (96.8)	52 (98.1)	19 (95)	0.227
If metabolic acidosis				
pH, median (IQR)	7.28 (7.18–7.34)	7.31 (7.28–7.36)	7.27 (7.22–7.32)	0.036*
Lactate, median (IQR), mmol/L	4.1 (2.96–8.15)	3.5 (2.55–4.75)	4.8 (3.88–7.12)	0.049*
If cardiac arrest				
Duration of code, median (IQR), min	30.5 (1–60)	60 (NA)	5 (NA)	1.00
Cumulative epinephrine, median (IQR), mg	0.15 (1–0.3)	0.3 (NA)	0.02 (NA)	1.00
Presence of compressions, n (%)	2 (100)	1 (100)	1 (100)	1.00
Age at first dose, median (IQR), days	0.64 (0.36–1.29)	0.92 (0.51–2.97)	1.32 (0.66–8.01)	0.013*
Weight at time of order, median (IQR), g	3043 (2778–3513)	3100 (2700–3585)	3195 (2625–3760)	0.897
Number of doses, median (IQR)	1 (1–3)	1 (1–3)	4 (3–5)	0.001*
Cumulative sodium bicarbonate dose, median (IQR), mEq/kg	2 (1–4.25)	2 (1–4)	6.5 (4.25–8)	0.001*
Total mEq of sodium bicarbonate/kg/day, n (%)				
Number of patients receiving >8 mEq/kg/day sodium bicarbonate	9 (14.5)	4 (7.5)	4 (20)	0.299
Time from last sodium bicarbonate dose to head imaging, median (IQR), hr	14.8 (5.5–37.67)	23.3 (9.1–101.58)	19 (4.78–107)	0.79
Thrombocytopenia 24 hr around head imaging, n (%)	16 (25.8)	13 (24.5)	7 (35)	0.653
INR >1.1 24 hr before or after head imaging, n (%)	19 (30.6)	22 (41.5)	9 (45)	0.488
Anticoagulation, n (%)				
Prophylactic	1 (1.6)	2 (3.8)	1 (5)	1.00
Therapeutic	0	0	2 (10)	1.00
Was anticoagulation ever supratherapeutic, n (%)	0	0	1 (5)	0.043
NSAID use, n (%)	0	0	1 (5)	0.056

INR, international normalized ratio; NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug

* Statistically significant.

Several mechanisms have elucidated the association between sodium bicarbonate administration and ICH, including the hyperosmolarity of concentrated sodium bicarbonate, hypernatremia from the sodium load, the carbon dioxide–generating properties of bicarbonate, and the rate of administration.[7–10,12,13] First, regarding the hyperosmolarity concern of sodium bicarbonate, a 1978 study by Papile et al[8] discussed this hypothesized mechanism as abrupt changes in serum osmolarity resulting in rapid shifts of fluid from the intracellular to the extracellular compartment. This shift leads to cell shrinkage and damage, which may lead to hemorrhage. However, Papile et al[8] only reviewed patients who had received dilute sodium bicarbonate, and they found lower rates of IVH compared with previous studies, suggesting that the use of sodium bicarbonate should be limited to dilute solutions given slowly. An increase in ICH due to the hyperosmolarity of sodium bicarbonate was also seen in a 1981 study by Sugimoto et al[9] in young and newborn rabbits following infusion with 7% sodium bicarbonate. Intracranial hemorrhage was observed in all cases where hyperosmolarity reached 392 mOsm/L (equal to 50 mL/kg), where the ICH was assessed immediately after death macroscopically.

Table 3. Primary and Secondary Outcomes*

	Only 4.2%	Only 8.4%	Mixed Group (Both 4.2% and 8.4%)	p value
Primary (n = 42), n	12	18	12	
ICH (baseline head imaging), n (%)	1 (8.3)	1 (5.6)	1 (8.3)	1.00
Secondary (n = 135), n	62	53	20	
ICH (no baseline head imaging), n (%)	7 (11.3)	2 (3.8)	2 (10)	0.325

ICH, intracranial hemorrhage

* Primary outcome: the incidence of ICH in patients with baseline and follow-up head imaging. Secondary outcome: the incidence of ICH on follow-up head imaging, with or without baseline head imaging.

The fluid shifts may lead to an increase in cerebral blood flow, showing a positive correlation with IVH in neonates who received sodium bicarbonate.[10] Although we assessed the incidence of ICH after administration of 2 different osmolarities of sodium bicarbonate (4.2% vs 8.4%), we did not find a significant difference.

Second, hypernatremia from the sodium load can lead to fluid shifts from the intracellular to extracellular compartments, which may lead to ICH. Simmons et al[14] demonstrated an increase in the incidence of IVH when daily intake of sodium was greater than 8 mEq/kg/day. In our population, of the 11 intracranial bleeds, 2 of the patients had received a daily intake of sodium greater than 8 mEq/kg/day (1 in the 4.2% group and 1 in the mixed group). There was a trend toward larger single (2–3 mEq/kg) and cumulative (1–9 mEq/kg) sodium bicarbonate doses in patients who had an ICH.

A third proposed mechanism is the carbon dioxide–generating property of sodium bicarbonate. Infusion of sodium bicarbonate results in the immediate formation of carbon dioxide, in which case an acid–base balance is produced as long as the lungs can remove excess carbon dioxide from the blood effectively. When there is impaired ventilation, such as during cardiac arrest, the addition of sodium bicarbonate moves the pH toward the apparent pK of 6.1, given the ratio of HCO_3^-/ CO_2 is closer to 1:1, as demonstrated by the Henderson-Hasselbach equation. Therefore, administering sodium bicarbonate to a patient with inadequate ventilation may worsen acidosis. A retrospective study investigating the short-term outcomes of sodium bicarbonate therapy in preterm infants found an increased risk of death and IVH with sodium bicarbonate administration (OR, 2.14; 95% CI, 1.65–2.77; $p < 0.001$). After adjusting for potential confounding factors (i.e., birth year, GA, sex, presence of pneumothorax, hypercarbia, red blood cell transfusion volume, highest serum sodium in the first 7 days of life), sodium bicarbonate infusion remained associated with an increased risk of death and IVH (OR, 1.27; 95% CI, 1.05–1.49; $p = 0.01$). However, the concentration of sodium bicarbonate used in these infants was not reported.[5] Another study of preterm infants found the incidence of IVH to be 10% in patients who received infusions of sodium bicarbonate during the first 24 hours of life, although the concentration used was also not reported.[6] Most of the patients in our study with ICH (n = 8) received mechanical ventilation prior to sodium bicarbonate administration, and several had a significant metabolic acidosis with a pH of 7.15 to 7.18, which may have contributed to cerebral damage.

Finally, looking into the rate of administration, a 2006 randomized controlled trial compared the effects of sodium bicarbonate given as a rapid bolus vs a slow infusion given during 30 minutes and evaluated the effects on cerebral hemodynamics and oxygenation in preterm infants. Increases in cerebral blood volume were seen in both cases, but the increase was more pronounced in the rapid bolus group, which may contribute to increases in ICH.[7] Missing information in the electronic record prevented us from evaluating this end point.

Caution should be exercised in applying these trial results to all neonates and infants because of the small sample size and retrospective nature of study. We could not confirm the rate of administration or the details surrounding sodium bicarbonate administration for cardiac arrest (duration of code, length of compressions, and cumulative dose of epinephrine). We do not teach our nurses to dilute sodium bicarbonate at the bedside; however, we could not confirm with certainty that the 8.4% formulation was not diluted at the bedside. Medications requiring bedside dilution are highlighted on the code sheet by each patient's bedside. There were also several recurring sodium bicarbonate shortages during the time frame of this study, leading to 4.2% being sequestered in the NICU, which may have led to selection bias. Additionally, our sample size for the primary outcome was limited, given the lack of routine head imaging outside of the NICU. Head imaging was only completed periodically when there was a specific concern or in accordance with an institutional standard (e.g., all patients admitted to the NICU; patients admitted to the CCVCU prior to all cardiac surgical interventions). Of note, data suggest that roughly 25% of term infants can have ICH without symptoms, and therefore our results may have been

confounded by the high baseline ICH prevalence, because baseline head imaging was not required for inclusion.[15] Furthermore, because patients less than 32 weeks' gestation are not admitted to the CCVCU, we excluded this group of patients and acknowledge that this is a limitation because they are at highest risk for ICH. It is important to take into consideration specific factors that could indicate the need for 4.2%, such as prematurity, hypoxic ischemic encephalopathy, head trauma, or individual/cumulative doses of sodium bicarbonate. For these reasons, institutions may consider stocking both formulations in the code cart, because larger multicenter trials are needed to assess the safety of 8.4% sodium bicarbonate in high-risk patients.

Conclusion

There was no statistical difference in the incidence of ICH in term neonates and infants receiving 4.2% vs 8.4% sodium bicarbonate. Although additional studies are needed, this study suggests it may be possible to safely expand the use of 8.4% in term neonates/infants. It is important to note that these results should not be applied to preterm neonates (<37 weeks GA and/or <1500 g) or neonates with additional risk factors for ICH.

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