Sodium Bicarbonate Use During Pediatric Cardiopulmonary Resuscitation: A Secondary Analysis of the ICU-RESUScitation Project Trial*

OBJECTIVES: To evaluate associations between sodium bicarbonate use and outcomes during pediatric in-hospital cardiac arrest (p-IHCA).

DESIGN: Prespecified secondary analysis of a prospective, multicenter cluster randomized interventional trial.

SETTING: Eighteen participating ICUs of the ICU-RESUScitation Project (NCT02837497).

PATIENTS: Children less than or equal to 18 years old and greater than or equal to 37 weeks post conceptual age who received chest compressions of any duration from October 2016 to March 2021.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Child and event characteristics, prearrest laboratory values (2–6 hr prior to p-IHCA), pre- and intraarrest hemodynamics, and outcomes were collected. In a propensity score weighted cohort, the relationships between sodium bicarbonate use and outcomes were assessed. The primary outcome was survival to hospital discharge. Secondary outcomes included return of spontaneous circulation (ROSC) and survival to hospital discharge with favorable neurologic outcome. Of 1,100 index cardiopulmonary resuscitation events, median age was 0.63 years (interquartile range, 0.19–3.81 yr); 528 (48.0%) received sodium bicarbonate; 773 (70.3%) achieved ROSC; 642 (58.4%) survived to hospital discharge; and 596 (54.2%) survived to hospital discharge with favorable neurologic outcome. Among the weighted cohort, sodium bicarbonate use was associated with lower survival to hospital discharge rate (adjusted odds ratio [aOR], 0.7; 95% CI, 0.54–0.92; $p = 0.01$) and lower survival to hospital discharge with favorable neurologic outcome rate (aOR, 0.69; 95% CI, 0.53–0.91; $p = 0.007$). Sodium bicarbonate use was not associated with ROSC (aOR, 0.91; 95% CI, 0.62–1.34; $p = 0.621$).

CONCLUSIONS: In this propensity weighted multicenter cohort study of p-IHCA, sodium bicarbonate use was common and associated with lower rates of survival to hospital discharge.

KEY WORDS: cardiopulmonary resuscitation; child; infant; neonate; sodium bicarbonate

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Cardiopulmonary resuscitation (CPR) for pediatric in-hospital cardiac arrest (p-IHCA) affects approximately 15,000 children in the United States every year (1, 2). During p-IHCA, children may develop metabolic acidosis due to tissue hypoxia, resultant anaerobic metabolism, and impaired renal perfusion (2). Historically, sodium bicarbonate has been used during CPR as a buffer to raise the extracellular pH in attempt to counteract the negative effects of metabolic acidosis. However, due to evidence of lack of benefit and potential harm, the American Heart Association (AHA) Pediatric

Advanced Life Support guidelines have recommended against the routine use of sodium bicarbonate in cardiac arrest since 2005 (3–9). Sodium bicarbonate may be administered for select scenarios including preexisting metabolic acidosis, hyperkalemia, or tricyclic antidepressant overdose (5–7). Despite these limited indications, two recent registry reports suggest sodium bicarbonate is still used frequently during p-IHCA and associated with decreased survival (10, 11).

Prior studies of sodium bicarbonate use during p-IHCA have been single-center or registry reports. Although important, these studies are limited due to their retrospective nature and level of detail reported. No multicenter prospective pediatric study has described hemodynamic data associated with sodium bicarbonate use during CPR. The primary objective of our study was to assess the relationships between sodium bicarbonate use during p-IHCA and outcomes. The primary outcome was survival to hospital discharge; secondary outcomes included return of spontaneous circulation (ROSC), survival to hospital discharge with favorable neurologic outcome, and functional status at hospital discharge. Further, we report child and event characteristics and pre- and intra-arrest hemodynamics associated with sodium bicarbonate use.

METHODS

The study is a prespecified secondary analysis of the ICU-RESUScitation (ICU-RESUS) project (NCT02837497). ICU-RESUS was conducted in 18 PICUs and pediatric cardiac ICUs (PCICUs) across 10 clinical sites from October 2016 to March 2021. Eight participating sites were affiliated with the Collaborative Pediatric Critical Care Research Network (CPCCRN). ICU-RESUS evaluated the effectiveness of a CPR quality improvement bundle on improving survival outcomes from ICU pediatric cardiac arrests (12). The bundle was comprised of physiology focused point-of-care CPR training and postcardiac arrest event debriefings. The institutional review board (IRB) at the University of Utah served as the single IRB and approved the study (no. 00093320) with waiver of parental permission.

Children were included in ICU-RESUS if they were less than or equal to 18 years old and greater than or equal to 37 weeks post conceptual age and received chest compressions of any duration in an ICU. Children were excluded if, prior to arrest, they had 1) pre-existing terminal illness and were not expected to survive the hospitalization, 2) documented lack of commitment to aggressive ICU therapies, 3) brain death, and 4) an out-of-hospital CPR event associated with the hospital admission. Additionally, children were excluded from this secondary analysis if extracorporeal membrane oxygenation (ECMO) was in use at the start of CPR. Of 1,129 index CPR events enrolled in ICU-RESUS, 29 received ECMO at the start of CPR leaving 1,100 events for this secondary analysis (**Supplemental Digital Content 1**, http://links.lww.com/PCC/C159). Of these, sodium bicarbonate was used in 528 events (48.0%) (**Table 1**).

TABLE 1.
Patient Characteristics by Sodium Bicarbonate Use

Characteristics	Sodium Bicarbonate Yes (*N* = 528)	Sodium Bicarbonate No (*N* = 572)
Demographics, *n* (%)		
Age		
≤ 1 mo	100 (18.9)	73 (12.8)
1 mo to < 1 yr	206 (39.0)	258 (45.1)
1 to < 8 yr	113 (21.4)	150 (26.2)
8 to < 19 yr	109 (20.6)	91 (15.9)
Male	293 (55.5)	296 (51.7)
Weight (kg), median (interquartile range)	7.2 (4.0–18.7)	6.8 (4.1–14.4)
Preexisting medical conditions, *n* (%)		
Respiratory insufficiency	440 (83.3)	505 (88.3)
Hypotension	399 (75.6)	294 (51.4)
Congestive heart failure	79 (15.0)	61 (10.7)
Pneumonia	56 (10.6)	78 (13.6)
Sepsis	104 (19.7)	74 (12.9)
Renal insufficiency	76 (14.4)	69 (12.1)
Malignancy	31 (5.9)	20 (3.5)
Trauma	18 (3.4)	16 (2.8)
Pulmonary hypertension	81 (15.3)	100 (17.5)
Congenital heart disease	325 (61.6)	307 (53.7)
Single ventricle heart disease	26 (4.9)	11 (1.9)

Data were collected at each site by trained research coordinators. Data included child and CPR event characteristics consistent with the Utstein Resuscitation Registry Template for In-Hospital Cardiac Arrest (13, 14). For children with invasive arterial catheters, hemodynamic waveforms were collected and reviewed and analyzed by investigators at the Children's Hospital of Philadelphia as previously described (15, 16).

Child characteristics included demographics and preexisting medical conditions. Preevent characteristics included illness category (medical cardiac, surgical cardiac, noncardiac), Pediatric Risk of Mortality (PRISM) score (17), Vasoactive Inotropic Score (VIS) (18), highest serum potassium concentration, and presence of hyperkalemia (potassium ≥ 6 mmol/L) 2–6 hr prior to CPR. Event characteristics included location of CPR, CPR duration, time of CPR (weekday/weeknight/weekend), first documented rhythm, immediate cause of cardiac arrest, interventions in place at start of CPR, open sternum at start of CPR, sternotomy procedure during CPR, and pharmacologic interventions during CPR. Post-CPR event data included use of ECMO within 6 and 24 hours of CPR and highest arterial lactate within 6 hours and between 6 and 24 hours and highest pH within 6 hours.

Hemodynamic variables included lowest systolic blood pressure 2–6 hours prior to CPR, average systolic and diastolic blood pressures 1 minute prior to CPR, and average systolic and diastolic blood pressures over the first minute and 10 minutes of CPR. Additional hemodynamic variables included average diastolic blood pressure greater than 25 mm Hg for children less than 1 year old and greater than or equal to 30 mm Hg for children greater than 1 year old and average systolic blood pressure greater than 60 mm Hg for children less than 1 yr old and greater than 80 mm Hg for children greater than 1 year old over the first 1 minute and 10 minutes of CPR.

The primary outcome was survival to hospital discharge. Secondary outcomes included ROSC, survival to hospital discharge with favorable neurologic outcome, functional status at hospital discharge in survivors, and presence of a new morbidity. Neurologic outcome was based on the Pediatric Cerebral Performance Category (PCPC). Favorable neurologic outcome was defined as PCPC score of 1 (normal), 2 (mild disability), or 3 (moderate disability) or no worse than baseline score (19). Functional outcome was assessed using the Functional Status Scale (FSS); absolute change from baseline to hospital discharge in survivors was reported (20). New morbidity was defined as worsening from baseline FSS by 3 or more points.

Statistical Analysis

Child and event characteristics were summarized with counts and percentages for categorical variables and medians and quartiles for continuous variables (Table 1 and **Supplemental Digital Content 2**, http://links.lww.com/PCC/C160). Differences in event characteristics between those with versus without sodium bicarbonate use were evaluated with Fisher exact test, Wilcoxon rank-sum test, and the Cochran-Armitage trend test, as appropriate. Hemodynamic variables were similarly reported by age (**Supplemental Digital Content 3**, http://links.lww.com/PCC/C161). Outcomes were summarized similarly but without statistical testing (**Table 2**) because a more careful analysis was warranted to account for potential confounding factors.

To assess the effect of sodium bicarbonate on outcomes, propensity weighted regression was used to reduce potential confounding from a priori factors (21). This robust approach involves three main steps. First, a logistic regression model of sodium bicarbonate use was created to estimate each subject's probability (propensity) for receiving sodium bicarbonate (**Supplemental Digital Content 4**, http://links.lww.com/PCC/C162). Variables included in the model were study site, age, illness category, sepsis, PRISM components, VIS, first documented rhythm, hypotension as immediate cause of arrest, and duration of CPR. A histogram of propensities was created for those with versus without sodium bicarbonate use (**Supplemental Digital Content 5**, http://links.lww.com/PCC/C163). Eleven subjects with a propensity for sodium bicarbonate use less than 0.02 and seven with propensity greater than 0.98 were excluded from further analysis because there were no comparable subjects in the opposite treatment group.

Second, subjects were weighted using stabilized inverse probability of treatment weights. This weighting increases the balance of a priori characteristics between those with versus without sodium bicarbonate use, creating a weighted cohort in which subjects differ with respect to sodium bicarbonate use but

TABLE 2.
Summary of Outcomes by Sodium Bicarbonate Use

Outcomes	Sodium Bicarbonate Use		
	Yes (*N* = 528)	No (*N* = 572)	Overall (*N* = 1,100)
Return of spontaneous circulation[a], *n* (%)	260 (49.2)	513 (89.7)	773 (70.3)
Survival to hospital discharge, *n* (%)	223 (42.2)	419 (73.3)	642 (58.4)
Survival to hospital discharge with favorable neurologic outcome[b,c], *n* (%)	202 (38.3)	394 (68.9)	596 (54.2)
Survival to hospital discharge with Pediatric Cerebral Performance Category of 1, 2, or no worse than baseline, *n* (%)	185 (35.0)	360 (62.9)	545 (49.5)
Change from baseline to hospital discharge in functional status of survivors[b], median (interquartile range)	1.0 (0.0–3.0)	1.0 (0.0–3.0)	1.0 (0.0–3.0)
New morbidity among survivors[d], *n* (%)	73/223 (32.7)	123/419 (29.4)	196/642 (30.5)

[a]Return of spontaneous circulation reported is the immediate outcome of the resuscitation event.
[b]Baseline Pediatric Cerebral Performance Category (PCPC) and Functional Status Scale represent child status prior to the event leading to hospitalization.
[c]Favorable neurologic outcome is defined as no more than moderate disability or no worsening from baseline PCPC.
[d] New morbidity among survivors is defined as a worsening from baseline functional status by 3 points or more.

are balanced with respect to potentially confounding characteristics (**Supplemental Digital Content 6**, http://links.lww.com/PCC/C164). This is the mechanism by which confounding from characteristics is reduced. Thus, the level of balance obtained is critical. Differences in means and proportions were compared between those with versus without sodium bicarbonate use. When means between groups differed by less than one-tenth of a SD, i.e. absolute standardized difference less than 0.10, the groups were considered well balanced (21).

Third, regression models were built using the weighted cohort to assess the effect of sodium bicarbonate on outcomes (**Table 3**). Ordinary linear regression was used for continuous outcomes, and logistic regression was used for binary outcomes. These models controlled for four a priori selected variables (first documented rhythm, age, illness category, and CPR duration) to further reduce potential confounding from these variables and reduce the unexplained variability in the models to improve power (22, 23). These models also controlled for variables that could not be balanced by the propensity score (Sites D and J and creatinine). All analyses were performed using SAS 9.4 (SAS Institute; Cary, NC) with reported *p* value based on a two-sided alternative and considered significant if less than 0.05.

RESULTS

Of 1,100 index CPR events, median age was 0.63 years (interquartile range, 0.19–3.81 yr); 589 events (53.5%) were in males, and the most common preexisting medical condition was respiratory insufficiency (Table 1). CPR event characteristics are shown in Supplemental Digital Content 2 (http://links.lww.com/PCC/C160). Sodium bicarbonate use was more common in medical cardiac and surgical cardiac patients than noncardiac patients. Sodium bicarbonate was used more often in children with higher PRISM and VIS scores. Few children (*n* = 30) had hyperkalemia, and sodium bicarbonate use was similar between those with and without hyperkalemia. Children with p-IHCA in a PCICU received sodium bicarbonate more often than those in a PICU. Longer CPR duration, pulseless electrical activity (PEA)/asystole, and ventricular fibrillation/tachycardia as the first documented rhythm and hypotension as the immediate cause of arrest were associated with sodium bicarbonate use. Sodium bicarbonate use was associated with having an open sternum at the start of CPR and sternotomy procedure during CPR. Sodium bicarbonate use was associated with additional pharmacologic interventions during CPR including epinephrine, atropine, calcium, vasopressin, amiodarone, lidocaine, and fluid boluses. Postarrest characteristics associated

TABLE 3.
Estimated Effect of Sodium Bicarbonate Use on Outcomes

Outcomes	Adjusted OR (95% CI)	Mean Difference (95% CI)	*p*
Return of spontaneous circulation[a]	0.91 (0.62–1.34)		0.621
Survival to hospital discharge	0.70 (0.54–0.92)		0.010
Survival to hospital discharge with favorable neurologic outcome[b,c]	0.69 (0.53–0.91)		0.007
Survival to hospital discharge with Pediatric Cerebral Performance Category of 1, 2, or no worse than baseline	0.80 (0.62–1.05)		0.105
Change from baseline to hospital discharge in functional status of survivors[b]		–0.39 (–0.90 to 0.13)	0.139
New morbidity among survivors[d]	0.67 (0.45–0.98)		0.038

OR = odds ratio.

[a]Return of spontaneous circulation reported is the immediate outcome of the resuscitation event.

[b]Baseline Pediatric Cerebral Performance Category (PCPC) and Functional Status Scale represent subject status prior to the event leading to hospitalization.

[c]Favorable neurologic outcome is defined as no more than moderate disability or no worsening from baseline PCPC.

[d]New morbidity among survivors is defined as a worsening from baseline functional status by 3 points or more.

Models were weighted using stabilized inverse probability of treatment weights and additionally controlled for site D, site J, creatinine, first documented rhythm, age, illness category, and cardiopulmonary resuscitation duration.

with sodium bicarbonate use included higher arterial lactate and ECMO cannulation within 6 hours of CPR and higher arterial lactate within 6–24 hours and ECMO cannulation within 24 hours.

Hemodynamic data by age and sodium bicarbonate use are shown in Supplemental Digital Content 3 (http://links.lww.com/PCC/C161). Children 1 month to less than 1 year old who received sodium bicarbonate were less likely to achieve average systolic blood pressure greater than or equal to 60 mm Hg during the first 10 minutes of CPR. Children 1 year to less than 8 years had lower systolic pressure 2–6 hours prior to CPR and lower average diastolic pressure during the first 10 minutes of CPR. Children 8 years to less than 19 years had lower average systolic pressure during the first minute of CPR.

Outcome data are reported in Table 2. Survival to hospital discharge occurred in 223 children (42.2%) who received sodium bicarbonate versus 419 (73.3%) who did not. Survival to hospital discharge with favorable neurologic outcome occurred in 202 (38.3%) who received sodium bicarbonate versus 394 (68.9%) who did not.

Sodium bicarbonate use varied by study site and was more likely with prearrest acidosis (pH < 7.0 or total Co_2 < 5, 2–6 hr prior to CPR), hypotension as the immediate cause of arrest, and longer duration of CPR (Supplemental Digital Content 4, http://links.lww.com/PCC/C162). Except for Site D and J, these variables were balanced in the propensity scoring (Supplemental Digital Content 6, http://links.lww.com/PCC/C164). Serum creatinine was also not balanced in propensity scoring. Therefore Site D, J, and serum creatinine were controlled for in models estimating the effect of sodium bicarbonate on outcomes. In addition, a priori selected variables including first documented rhythm, age, illness category, and duration of CPR were controlled for in these models. Estimates of the effect of sodium bicarbonate on outcomes among the weighted cohort are shown in Table 3. Sodium bicarbonate use was not associated with ROSC. Sodium bicarbonate use was associated with decreased survival to hospital discharge and decreased survival to hospital discharge with favorable neurologic outcome. Sodium bicarbonate use was also associated with less new morbidity among survivors.

DISCUSSION

In this contemporary multicenter analysis, we found that sodium bicarbonate is used frequently during p-IHCA and that its use is associated with worse outcomes including decreased survival to hospital discharge and decreased survival with favorable neurologic outcome. Sodium bicarbonate use was associated with child and event characteristics including cardiac diagnoses, greater illness severity, and longer CPR duration. Sodium bicarbonate use was not associated with improved hemodynamics during CPR or greater likelihood of ROSC.

Despite limited AHA indications for sodium bicarbonate during p-IHCA, it was administered in almost half of CPR events in our study. Two previous registry studies reported similar findings. Raymond et al (10) analyzed 3,719 pediatric index CPR events from 2000 to 2010 using data from the AHA's Get with the Guidelines Registry and found sodium bicarbonate was used in 68% of events and associated with decreased ROSC, decreased survival to discharge, and decreased survival with favorable neurologic outcome. Loomba et al (11) focused primarily on pediatric cardiac patients using data from the Pediatric Health Information System to determine patient characteristics, outcomes, and billing charges associated with sodium bicarbonate use during CPR from 2004 to 2015. In this study, 3,987 (50.3%) used sodium bicarbonate; however, use decreased from 62.1% to 43.7% over the period of study. Sodium bicarbonate use was associated with increased mortality consistent with our findings. Our results support a declining use of sodium bicarbonate when compared with earlier reports; however, sodium bicarbonate is still used frequently and likely outside of AHA recommendations.

Similar to previous work, we found sodium bicarbonate use was associated with decreased survival to hospital discharge, decreased survival with favorable neurologic outcome, and no difference in ROSC (8–10, 24–29). We also unexpectedly observed sodium bicarbonate use was associated with less new morbidity in survivors. Outcomes of p-IHCA range from mortality at one extreme, to survival with new morbidity in the middle, to intact survival at the other extreme. If sodium bicarbonate disproportionately shifts outcome among children who might otherwise have survived with new morbidity toward higher mortality, then this middle group may be smaller as a result.

We used propensity weighted analysis to account for many variables that could confound the relationship between sodium bicarbonate use and outcome. For example, prior studies by Raymond et al (10) and Meert et al (9) showed that sodium bicarbonate administration was associated with longer CPR duration even when excluding extremes (CPR events < 5 min or > 120 min), and longer CPR duration was associated with mortality. These authors suggest that sodium bicarbonate is often used as a "last-ditch" effort for patients who are unlikely to survive (9). In our study, to reduce the confounding effect of CPR duration, we included CPR duration in the propensity model and as a covariate in the final multivariable models. Using this doubly robust approach (22, 23), we found that sodium bicarbonate use was associated with worse outcomes. However, we were not able to perform time-dependent propensity matching because the time of sodium bicarbonate administration was not available in the ICU-RESUS dataset. We also included illness category (medical cardiac, surgical cardiac, and noncardiac) in the propensity model and as a covariate to reduce confounding by cardiac diagnoses.

Mechanisms underlying increased mortality with sodium bicarbonate use are not entirely clear but include hyperosmolarity, hypokalemia, hypocalcemia, hypernatremia, intracellular acidosis, and impaired tissue oxygen delivery if administered excessively (30–33). Our findings suggest that sodium bicarbonate should be used with caution during CPR if at all.

Sodium bicarbonate use varied by clinical site, illness category, and location of care (PCICU vs PICU). This likely reflects important center and provider variation and attitudes about administration of sodium bicarbonate despite limited data to support its use (24). Children who received sodium bicarbonate had higher PRISM and VIS scores, longer CPR duration, and greater likelihood of additional resuscitation medications, PEA/asystole, ventricular tachycardia or fibrillation, and hypotension as the immediate cause of arrest than those not receiving sodium bicarbonate similar to previous reports (9, 10).

Unlike previous reports, we were able to assess hemodynamics in the period immediately preceding and during CPR. In children greater than 1 month old, there were some differences in hemodynamic variables during CPR between treatment groups, with lower systolic and/or diastolic blood pressures in those that received sodium bicarbonate. However, since the timing of sodium bicarbonate administration was not recorded and all intra-arrest hemodynamics were within the first 10 minutes of CPR, it is possible that sodium bicarbonate was administered after these intra-arrest hemodynamic measurements. Only children 1 year old to less than 8 years treated with sodium bicarbonate had lower systolic blood pressures 2–6 hours prior to CPR. Although statistically significant, these minor differences in hemodynamics between treatment groups are of unclear clinical significance. Because of the lack of data on timing of sodium bicarbonate, the extent to which sodium bicarbonate use during CPR was driven by hemodynamic responsiveness cannot be determined.

Strengths of this study include the multicenter design, prospective data collection, and robust statistical approach for reducing confounders. Although many important confounders were controlled for in our analyses, others may exist that were not collected. A major limitation is that the time of sodium bicarbonate administration was not collected. Thus, we were unable to perform time-dependent propensity matching, an approach to delineate effects of time-sensitive CPR interventions (34, 35). Other limitations include the lack of intra-arrest laboratory values (e.g., potassium, pH); values collected 2–6 hours prior to CPR may not reflect those during CPR. Thus, we were not able to assess whether bicarbonate use for severe intra-arrest metabolic acidosis (e.g., pH < 7.0 or < 7.1) was associated with better or worse outcomes. Hemodynamic waveforms could only be collected from children with invasive arterial catheters. Indications for sodium bicarbonate and total dose were not recorded. The majority of children included in our study were infants (< 1 yr) potentially limiting the ability to generalize findings to older age groups. All ICUs participating in our study were academic centers potentially limiting the ability to generalize to nonacademic sites. Importantly, this is an observational study, and the associations observed do not infer causation. Future directions include investigating the timing of sodium bicarbonate administration in relation to intra-arrest hemodynamics and the use of sodium bicarbonate in specific subgroups that may have high potential to benefit such as severe intra-arrest acidosis and hyperkalemia.

CONCLUSIONS

In this propensity weighted multicenter cohort study of p-IHCA, sodium bicarbonate was used in 48% of CPR events and was associated with lower rates of survival to hospital discharge.

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