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Original Contributions

Sodium bicarbonate improves outcome in prolonged prehospital cardiac arrest☆

Rade B. Vukmir MD, JD, FCCP, FACEP*, Laurence Katz MD
Sodium Bicarbonate Study Group[1]

University of Pittsburgh Medical Center Northwest; and the Safar Center for Resuscitation Research, Pittsburgh, PA 16346, USA

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Abstract

Objective: This study evaluates the effect of early administration of an empirical (1 mEq/kg) sodium bicarbonate dose on survival from prehospital cardiac arrest within brief (<5 minutes), moderate (5-15 minutes), and prolonged (>15 minutes) down time.

Methods: Prospective randomized, double-blinded clinical intervention trial that enrolled 874 prehospital cardiopulmonary arrest patients managed by prehospital, suburban, and rural regional emergency medical services. Over a 4-year period, the randomized experimental group received an empirical dose of bicarbonate (1 mEq/kg) after standard advanced cardiac life support interventions. Outcome was measured as survival to emergency department, as this was a prehospital study.

Results: The overall survival rate was 13.9% (110/792) for prehospital arrest patients. There was no difference in the amount of sodium bicarbonate administered to nonsurvivors (0.859 ± 0.284 mEq/kg) and survivors (0.8683 ± 0.284 mEq/kg) (P = .199).

Overall, there was no difference in survival in those who received bicarbonate (7.4% [58/420]), compared with those who received placebo (6.7% [52/372]) (P = .88; risk ratio, 1.0236; 0.142-0.1387). There was, however, a trend toward improved outcome with bicarbonate in prolonged (>15 minute) arrest with a 2-fold increase in survival (32.8% vs 15.4%; P = .007).

Conclusion: The empirical early administration of sodium bicarbonate (1 mEq/kg) has no effect on the overall outcome in prehospital cardiac arrest. However, a trend toward improvement in prolonged (>15 minutes) arrest outcome was noted.

1. Introduction

It is difficult to predict the outcome from prehospital cardiac arrest because of a diversity of arrest populations. Becker et al [1] published a thought-provoking article in 1991 that reported a realistic survival rate to hospital discharge of only 1.7% in the large (3224-patient) urban study, compared with a historic range of survival from 1% to 33%.

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* Corresponding author. Tel.: +1 814 676 7863; fax: +1 814 676 7975.
E-mail address: rbvmd@comcast.net (R.B. Vukmir).
[1] See Appendix.

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Variability in survivorship is explained in several ways. Valenzuela et al [2] analyzed prehospital arrests and noted that using various case definitions, arrest outcome finds a 20% hospital survival, improving to 26% for witnessed arrests, and 38% for arrests both witnessed and in ventricular fibrillation, a notable improved outcome group. However, the overall survival rate did decrease from 20% to 6% by the time of hospital discharge. There is significant variability across various geographic areas. Lombardi et al [3] evaluated 2071 patients and found an overall survival to discharge of 1.3% with poor outcome in the urban environment, presumptively related to transport issues.

Risk stratification has been used to attempt to predict outcome. Findings such as a return of spontaneous circulation (ROSC) are suggested by Kellerman et al in evaluation of 1068 out-of-hospital arrests to be associated with subsequent survival [4]. They find an ROSC rate of 29% in the field that correlates with increased likelihood of survival to admission (69% vs 7%; $P < .01$) and subsequent hospital discharge (26.5% vs 0.4%; $P < .01$).

Later, Shuster and Chong [5] evaluated 15 prehospital studies during the early years of emergency medical care, suggesting no benefit of prehospital administration of any of several commonly administered prehospital medications. Qualitatively, there have been few studies that have examined the use of such commonly used prehospital agents as albuterol, bicarbonate, diazepam, dobutamine, dopamine, glucose, isoproterenol, naloxone, or nitrous oxide for their efficacy [6].

Four factors have been related to the ability to resuscitate patients in the prehospital arrest setting including time to starting rescue procedures, use of electrical defibrillation, accuracy of technique of basic life support (BLS), and ventilation efficacy [7].

There has been little outcome information available on the use of sodium bicarbonate in prehospital cardiac arrest patients. Theoretical benefit has been described for the use of bicarbonate in prolonged arrest, as well as improved outcome in a canine model of ventricular fibrillation arrest with a 15-minute or greater down time [8,9].

2. Methods

This prospective, randomized multicenter clinical trial involved cardiac arrest patients encountered by emergency medical technician-paramedics (EMT-Ps) in a prehospital setting and transported to hospitals within the study area, usually within a 5- to 30-minute transport radius. The multicenter trial enrolled patients encountered by Western Pennsylvania emergency medical service (EMS) systems into this protocol, over a 4-year period from 1994 to 1998.

This networking used 7 different EMS systems operating under a standing-order protocol system, with capability for physician consult. This was a single-tier paramedic response system operating in rural, suburban, and urban environments before the advent of first responder early defibrillation.

Inclusion criteria enrolled those subjects suffering cardiac arrest refractory to defibrillation, in whom intravenous (IV) access was obtained. Exclusion criteria included those subjects suffering overt respiratory such as chronic obstructive pulmonary disease or traumatic arrest, children (<18 years), and after multiple failed attempts, those without IV access. Patients received standard advanced cardiac life support (ACLS) protocol including chest compressions, ventilation, defibrillation, epinephrine (0.01 mg/kg), atropine (0.01 mg/kg), and antiarrhythmics or pressor agents, as warranted. All patients were randomized to a treatment group receiving an empirical dose of bicarbonate (Abbott Laboratories, Chicago, Ill) 1 ample (50 mEq/L) early in the arrest cycle or the control group who received an equal amount of normal saline in a double-blinded fashion to clarify the benefits of the osmolar load vs base deficit correction. Randomization was accomplished by blinded packaging by the manufacturer (Abbott Laboratories), and every patient received study intervention.

Routine demographic and clinical variables related to outcome were analyzed including demographics, response to bicarbonate administration, scene factors, response time, cardiopulmonary variables, procedures, and duration of arrest (Table 1). Routine cardiopulmonary variables were monitored. Patient outcome was recorded as the ROSC (mean atrial pressure of 50 mm Hg) and initial ED survival defined as presenting with a pulse to the ED.

Specifically, resuscitation intervention times were recorded by the EMT-P as estimated time (ET) of arrest

Table 1 Prehospital variables potentially correlated to survival

Demographics
Age, weight, sex
Response time
ET arrest, ET ByCPR, ET BLS, ET ACLS, ET ROSC, ET Hosp
Interventions
Bicarbonate (dose, weight-based)
Scene factor
Bystander CPR, witnessed
Cardiopulmonary variables
Initial rhythm, ISBP, IDBP
Procedures
Intubation, IV, others
Duration of arrest
Short (<5 min), moderate (5-15 min), long-term (>15 min)
EMS coverage
Urban, suburban, rural
Past medical history
MI, HTN, DM, CHF, COPD, CABG
Medication
Cardiac, HTN, arrhythmia, pulmonary, hematologic, GI, psychiatric, seizure

ISBP, initial systolic blood pressure; IDBP, initial diastolic blood pressure; MI, myocardial infarction; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass graft; HTN, hypertension; GI, gastrointestinal; DM, diastolic murmur.

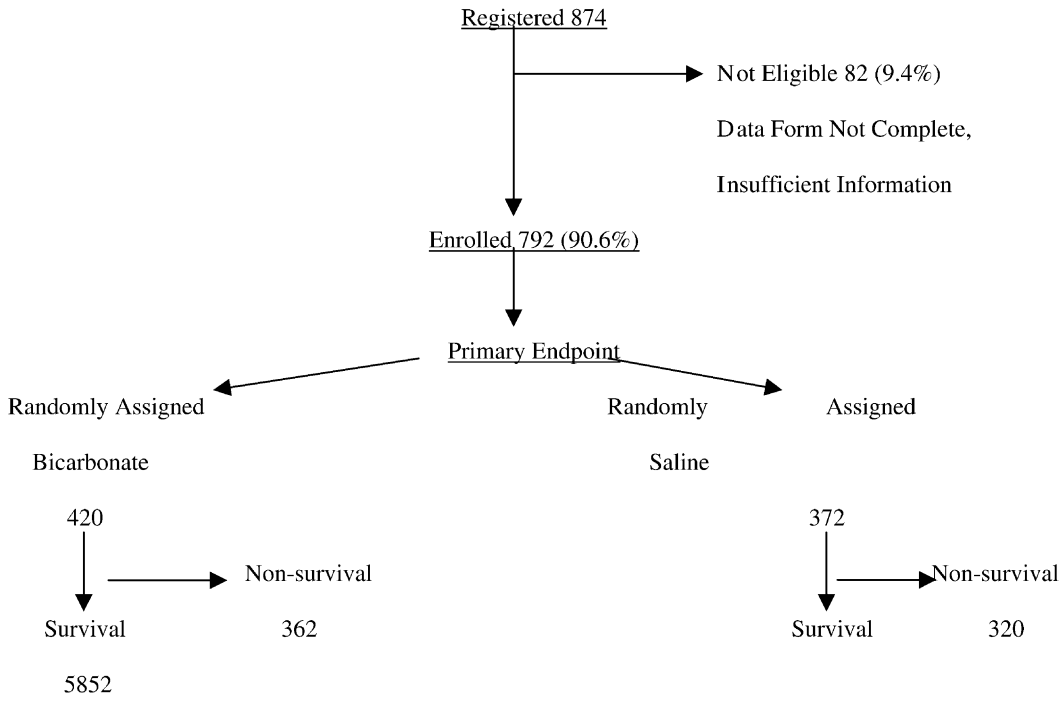

Fig. 1 Trial profile.

(ET arrest), time until institution of bystander cardiopulmonary resuscitation (CPR) (ET ByCPR), BLS (ET BLS), ACLS (ET ACLS), ROSC (ET ROSC), and scene to hospital transport time (ET TT). In addition, ACLS intervention time based on the length of resuscitative effort is subcategorized into short-term (0-15 minutes) and long-term (>15 minutes) responses for further analysis.

Examining these same issues according to the Office for Protection from Research Risk Guidelines suggests further qualification to waive prospective informed consent according to the second waiver condition of 45 CFR 46.116 section D [10], as follows: (1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects were provided with additional information after participation.

Numerical data were represented as mean and SD with Student t test, Fisher exact, and χ^2 with Pearson correction tests used for intergroup comparisons ($\alpha < 0.05$) using the SPSS/PC+ statistical system (Chicago, Ill), where appropriate. The overall study results were examined by the investigators at 3-month intervals (or 25% of projected patients) to verify early trends and outcome with capability of later modification.

The sample size of 1000 was sufficient to delineate a 50% difference in survival at 80% power and a 95% confidence interval between control and treatment groups. This estimate was based on a 12% rate of ROSC in the city prehospital arrests.

3. Results

There were 874 patients enrolled with 82 (9.4%) not eligible because of failure of documentation or data collection. The overall survival rate was 13.9% (110/792) for prehospital cardiac arrest patients (Fig. 1). There was no difference in mean patient age, weight, or amount of bicarbonate or saline control administered (Table 2).

The effect of increased body weight adversely impacted outcome. Although, there was no difference of age on survivorship. Nonsurvivors were found to have a roughly

Table 2 Demographic data correlated to bicarbonate or saline administration

	Control	Bicarbonate	Significance (P)
Age (y)	67.16 ± 14.96	67.37 ± 15.29	.770
n	372	418	
Weight (kg)	87.87 ± 33.39	89.73 ± 42.74	.515
n	346	395	
Sodium bicarbonate or normal saline	69.56 ± 22.32	69.82 ± 22.17	.877
Amount (mEq or mL)	336	175	
n			
Weight-based (mEq or mL/kg)	.85 ± .29	.84 ± .26	.596
n	155	175	

Table 3 Demographics correlated to survival

	Nonsurvival	Survival	Significance (*P*)
Age (y)	67.34 ± 14.88	67.45 ± 15.22	.943
n	654	109	
Weight (kg)	84.86 ± 27.25	77.32 ± 21.35	.002
	602	105	
Sodium bicarbonate Amount (mEq)	70.37 ± 22.27	62.73 ± 21.48	.001
	648	108	
Weight-based (mEq/kg)	0.859 ± 0.284	0.8088 ± 0.265	.199
	280	56	

10% increase in body weight (84.9 ± 27.3 vs 77.3 ± 21.4 kg; $P = .002$), compared with those who survived (Table 3).

There was also a significant difference in survival based on the total amount of bicarbonate administered with increased mortality in those who received a greater total dose (70.4 ± 22.3 vs 62.7 ± 22.8 mEq; $P = .001$). However, this difference dissipated when weight-based dosing considerations were included with a dose of 0.86 ± 0.28 mEq/kg in nonsurvivors, compared with 0.809 ± 0.26 mEq/kg ($P = .199$) in survivors.

Overall, there was no difference in survival in those who received bicarbonate 13.8% (58/420), compared with the control group who received normal saline instead (13.9% [52/372]) (Table 4). However, there was a trend toward improvement with bicarbonate in prolonged prehospital cardiac arrest, specifying the duration of resuscitative effort; there was a 2-fold increase in survival (32.8% vs 15.4%; $P = .007$) noted in arrests more than 15 minutes in duration (Table 5).

4. Discussion

Historically, the focus of cardiac arrest therapy has changed. Early resuscitative efforts in the 60s emphasized therapy in arrest directed toward correcting metabolic acidosis using sodium bicarbonate to combat the ongoing metabolic derangement. Development of resuscitation techniques over the next half century suggested that respiratory concerns were paramount, and the acidosis of arrest, if important at all, could be reversed by aggressive hyperventilation.

This philosophy was embodied in the Standards and Guidelines for CPR and Emergency Cardiac Care, which, in 1980, first suggested the empirical administration of bicarbonate, with dosing based on systemic arterial acidosis and, finally, in 1986, curtailed empirical administration of bicarbonate, except in certain circumstances [11,12]. The 1996 guidelines suggest a complex decision tree for the use of bicarbonate based on presumed efficacy or lack thereof in specific circumstances [13].

The use of sodium bicarbonate was categorized as follows: class I, if known preexisting hyperkalemia; class IIa, if known preexisting bicarbonate-responsive acidosis (eg, diabetic ketoacidosis) or overdose (eg, tricyclic antidepressant overdose, cocaine, diphenhydramine) to alkalinize urine; class IIb, if prolonged resuscitation with effective ventilation upon ROSC after long arrest interval; and class III, (not useful or effective) in hypercarbic acidosis (eg, cardiac arrest and CPR without intubation) [13].

More recent evidence-based recommendations are less specific, recommending class I interventions as always acceptable; IIa/IIb, acceptable, safe, and useful with IIa the standard of care and IIb with the standard of care and indeterminate that can still be recommended for use but with less research support [14]. Here, bicarbonate was

Table 4 Bicarbonate correlation to ED survival

Bicarbonate	ED survival		
	No	Yes	
No	320	52	372
	86.0%	13.9%	
Yes	362	58	420
	86.1%	13.8%	
	682	110	792
	86.1%	13.9%	100.0%

χ^2 with Pearson correction; $P = 1.0$; risk ratio, 1.0122.

Table 5 ED survival and bicarbonate time to ACLS

	Time to ACLS	Brief-moderate	Prolonged	
		0-15	15+	Total
Survival				
Yes bicarbonate	n	39	19	58
	% with ED survival and bicarbonate	67.2%	32.8%	100.0%
No bicarbonate	n	44	8	52
	% with ED survival and bicarbonate	84.6%	15.4%	100.0%
Nonsurvival				
Yes bicarbonate	n	223	139	362
	% with ED survival and bicarbonate	61.6%	38.4%	100.0%
No survival/no bicarbonate	n	193	127	320
	% with ED survival and bicarbonate	60.3%	39.7%	100.0%
Total	n	499	293	792
	% with ED survival and bicarbonate	63.0%	37.0%	100.0%

χ^2 test with Pearson correction; $P = .007$.

recommended as "consider buffers" for ventricular fibrillation/pulseless ventricular tachycardria, pulseless electrical activity, and asystole.

They caution that bicarbonate therapy should be administered in a 1-mEq/kg initial dose, guided by the bicarbonate concentration or calculated base deficit and avoiding full correction to avoid chances of iatrogenic alkalosis [14].

Evidence supporting these changes has been suggested by predominantly theoretical considerations or recommendations from uncontrolled studies. These include the description of "paradoxical cerebral spinal fluid acidosis" or the coronary and systemic venous paradox [15,16]. These theoretical constructs suggest that because of the preferential diffusion of carbon dioxide compared with HCO_2 in arrest, the cellular pH may be rendered more acidotic if bicarbonate is administered because of excess carbon dioxide accumulation.

Animal studies have suggested adverse outcome in lactic acidosis when bicarbonate was administered, but only for high-dose models [17]. Human studies have described alkalosis and its negative effect on mortality retrospectively, but the qualitative relation to the amount of exogenous bicarbonate administered is unclear [18]. Another large trial of cardiac arrest finds that patients who received a "nonstandard" protocol in which bicarbonate administration was included had a decreased survival, compared with patients who were resuscitated according to the current ACLS recommendations (3.6% vs 12.3%) [19]. However, bicarbonate administration was only a single factor in a host of protocol alterations.

Historically, the debate over the use of bicarbonate in lactic acidosis was summarized by the discussion of Stacpoole [20], who suggested significant adverse metabolic and cellular effects, whereas the rebuttal by Narins and Cohen [21], which offered a more controlled evaluation of bicarbonate in human cardiac arrest, has demonstrated an adverse effect on survival. However, a canine model of cardiac arrest found significant benefits in survival and neurologic outcome after 5, 10, and 15 minutes of arrest [22,23].

Thus, the use of bicarbonate in arrest is controversial. Current recommendations suggest that bicarbonate should not be used without effective ventilation in those patients with compromised pulmonary function for arrests of brief duration or in repetitive doses without confirmation of acidosis [24]. If it is used, then aggressive hyperventilation and frequent pH monitoring, as well as reduction of total dose, should be instituted [25]. The recommendation for ACLS instruction was succinct: "use if at all, only after application of more definitive and better substantiated interventions, even in unwitnessed arrest [26]." This constitutes the standard of cardiac arrest therapy to this day, with little modification.

There is little in the way of hard clinical scientific evidence concerning the effect of bicarbonate on arrest outcome. Aufderheide [27] evaluated 215 prehospital arrest cases given an average of 79.1 (25-200 mEq) of bicarbonate and finds no increase in adverse side effects and decreased metabolic acidosis in prolonged (>15 minutes) arrest times.

Likewise, VanWalraven [28] performed a secondary analysis of 773 adults noting that bicarbonate was administered to 19% of survivors and 42% ($P < .001$) of nonsurvivors. They report odds ratios of survival of 0.08 for epinephrine, 0.24 for atropine, 0.31 for bicarbonate, 0.32 for calcium, 0.48 for lidocaine, and 0.55 for bretylium with no medication associated with increased survival.

Weaver et al [29] evaluated 199 patients with persistent ventricular fibrillation refractory to defibrillation and epinephrine administration. The resuscitation rate improves when associated with bicarbonate infusion (64% vs 52%), compared with 500 historical control patients, although the overall survival rate (24% vs 20%) is unchanged. This certainly is significant clinically, not statistically.

The overall survival rate of 13.9% (110/792) compares favorably with a 4.2% (1.7%-13%) rate from pooled analysis of 3220 prehospital patients, suggesting improved outcome [30]. The per-experimental study groups were found to be equivalent undergoing adequate randomization resulting in similar demographic groups and treatment interventions minimizing selection bias.

The isolated findings of the adverse effect of body weight and increasing bicarbonate dose on outcome are minimized by the equivalent outcome in weight-based administrating dosing strategies. A single unifying hypothesis may suggest that incremental weight-based mEq/kg dosing may mitigate adverse effects of excessive bicarbonate dosing in smaller victims.

Another important consideration in the empirical dosing strategy of bicarbonate is to use the intervention in the presumptive high-incidence acidosis population usually found in prolonged arrest. This potentially allows us to explain the failure to find a difference in overall outcome when empirical bicarbonate is administered to all arrest patients. This may be due to a type II error, largely concluding that no significant difference exists between populations secondary to small sample size of 5-, 10-, and 15-minute arrest groups. However, when we subcategorize based on "down time," smaller clinical differences become more apparent. The most notable clinical improvement, a 2-fold increase in survivorship (32.8 vs 15.4%; $P = .007$), was noted in prolonged arrest associated with 15-minute or greater delay in ACLS intervention. This result might be anticipated in light of presumed anaerobic metabolism conditions associated with longer arrest times.

Acid base status can be inferred from a cardiac V-fib arrest model for comparison which finds the 5-minute arrest model is associated with an arterial pH of 7.22 ± 0.1 and venous pH of 7.09 ± 0.12, while the 15 minute arrest model found a pH A of 7.11 ± 0.15 and pH V of 6.93 ± 0.8, as opposed to measuring the pH which would be too late to be beneficial.

This study is limited by a moderate sample size and the deviation in defining outcome from the Utstein style of reporting [30].

5. Conclusion

We conclude that, if any, the most beneficial effect is found in those with arrests of prolonged down time (>15 minutes). Caution is warranted if bicarbonate is administered to those of more brief resuscitation delay because no benefit was achieved and theoretical harm can occur.

Appendix A. Sodium Bicarbonate Study Group

Primary Investigators: Rade B. Vukmir, MD; Laurence Katz, MD

Beaver: Paul Peindl, MD; Charles Bowers, EMT-P; Joseph Campbell, EMT-P

Greensburg: John Reed, MD; William Groft, EMT-P

Indiana: Steve Bashor, MD; James Dixon, MD; BJ Pino, EMT-P

McKees Rocks: Peter Stevenson, MD; Anthony Sanvito, EMT-P

Monessen: Frank Hertzog, MD; Bill Hess, EMT-P; Mark Sellew, EMT-P; Mark Eglgi, EMT-P

Monroeville: Dave Natale, MD; Doug Nicole, EMT-P

Pittsburgh: Michael Sullivan, MD; Uwe Ebmeyer, MD; Nicholas Bircher, MD; Paul Paris, MD; James Menegazzi, PhD; Peter Safar, MD

Sewickley: J Nagan, MD; J Withee, EMT-P

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