Critical Review Form
Therapy

PGY-4

Ahn S, Kim YJ, Sohn CH,et al. Sodium bicarbonate on severe metabolic acidosis during prolonged cardiopulmonary resuscitation: a double-blind, randomized, placebo-controlled pilot study. J Thorac Dis. 2018 Apr;10(4):2295-2302.

Objectives: **"to evaluate the effects of sodium bicarbonate with transient hyperventilation on the outcome of OHCA adult patients who failed to achieve ROSC [return of spontaneous circulation] and with severe metabolic acidosis (pH <7.1 or bicarbonate <10 mEq/L) after 10 minutes of CPR performed in the emergency department (ED) following OHCA resuscitation attempts." (p. 2296)**

Methods: **This prospective, randomized controlled trial was conducted between January 1, 2015 and December 31, 2015 at the Asan Medical Center in South Korea. Patients who failed to achieve ROSC after 10 minutes of CPR in the ED who had a severe metabolic acidosis (pH < 7.1 or bicarbonate < 10 mEq/L on arterial blood gas [ABG]) were eligible for enrollment. Exclusion criteria included a do-not-resuscitate order and need for extracorporeal CPR. The ABG was obtained after 10 minutes of CPR in the ED and run as a point-of-care test.**

Patients were randomized in a 1:1 fashion to receive either sodium bicarbonate (50 mEq) or normal saline (50 mL) injected over 2 minutes. In order to ameliorate the increased carbon dioxide burden associated with bicarbonate administration, the ventilatory rate was increased from 10 to 20 breaths per minute for 2 minutes after study drug administration. A repeat ABG was obtained after 20 minutes of CPR.

The primary outcome was the change in acidosis (i.e. difference in 10 minute and 20 minute pH and bicarbonate). The secondary outcome were sustained ROSC, survival to hospital admission, and survival with good neurologic outcome at 1 and 6 months (defined as a cerebral performance category [CPC] score of 1 or 2).

Out of 157 patients screened for enrollment, 50 were enrolled in the study with 25 in the bicarbonate group and 25 in the control group. Of these, 72% and 84% were male, respectively, and the median ages were 65.5 and 64.1 years.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. Patients were randomized in a 1:1 fashion to receive either sodium bicarbonate (50 mEq) or normal saline (50 mL) injected over 2 minutes.

2.	Was allocation concealed? In other words, was it possible to subvert the randomization process to ensure that a patient would be “randomized” to a particular group?	Uncertain. The authors report that, "A research associate generated a random sequence using Excel software..." (p. 2296) but fail to report how this sequence was used to allocate patients to their groups, who obtained or administered the study medication, or how clinicians were blinded to group allocation.
3.	Were patients analyzed in the groups to which they were randomized?	Presumably yes. While the authors do not specifically mention performing an intention to treat analysis, they also do not mention any crossover between groups and nobody was excluded after randomization. Presumably all patients received the treatment to which they were assigned.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Mostly yes, although the small sample size makes this interpretation difficult. Patients in the control group were more likely to be male than those in the bicarbonate group (84% vs. 72%), and less likely to be in a shockable rhythm prior to ED arrival (12% vs. 28%). They were similar with respect to medical comorbidities.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	Presumably no. The authors mention that this was a "double-blind" trial, but do not specify how blinding was ensured (i.e. unmarked vials with identical volume and appearance).
2.	Were clinicians aware of group allocation?	See above.
3.	Were outcome assessors aware of group allocation?	Uncertain. For the primary outcome and ROSC in the ED, the limitations above would still hold. It is unclear who evaluated survival to hospital discharge or neurologic outcomes at 1 and 6 months, and whether they were blinded to group allocation.
4.	Was follow-up complete?	Presumably yes. The authors do not mention any missing outcome data.
II.	**What are the results ?**	

1.	How large was the treatment effect?	• While there was no significant difference in pH or bicarbonate results between groups at 10 minutes, both measures were higher in the control group compared to the bicarbonate group:
		  ○ pH: 6.99 (95% CI 6.92-7.12) vs. 6.90 (95% CI 6.85-6.94); p = 0.038
		  ○ Bicarbonate: 21.00 (95% CI 15.85-28.75) vs. 8.00 (3.30-14.00); p = 0.007

		• There was no significant difference in pCO2 levels at 10 or 20 minutes. • There was no statistically significant difference in rates of sustained ROSC or survival to hospital admission between the bicarbonate and control groups, despite a large trend towards better outcomes in the control group: 4.0% vs. 16.0%, RR 0.25 (95% CI 0.03 to 2.2). • There was no significant difference in survival with good neurologic function at 1 month (RR 0, 95% CI 0 to ∞), and no patients in either group survived with good neurologic function at 6 months.
2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Likely yes. This study enrolled patients with OHCA who did not achieve ROSC within 10 minutes of ED arrival. While this study was conducted in South Korea, where the prevalence of obesity and medical comorbidities may be different from our institution, it seems unlikely that this would change the effect of bicarbonate on the outcomes (external validity).
2.	Were all clinically important outcomes considered?	Yes. While the primary outcomes (change in pH and bicarbonate level) are not patient-centered, the authors did also consider long-term functional outcomes.
3.	Are the likely treatment benefits worth the potential harm and costs?	No. While this is a small, pilot study and will need to have its results verified in a larger trial, the results here suggest that while bicarbonate administration on prolonged OHCA may improve non-patient-centered outcomes, they do not have any benefit in terms of survival or survival with a good neurologic outcome.

Limitations:

1. **This article was significantly limited by underreporting:**
    a. **There is no mention of how the randomization sequence was used to perform group allocation (allocation concealment).**
    b. **There is no mention of how patients and clinicians were blinded to group allocation.**

c. **There is no mention as to how 1 and 6 month neurologic outcomes were determined.**

d. **The authors do not mention whether an intention to treat analysis was performed.**

2. **Two cointerventions were performed (increased ventilatory rate and administration of bicarbonate). Both interventions could conceivably affect outcomes and yet there is no means of identifying what effect each individual intervention would have.**

3. **The primary outcome (the change in pH or bicarbonate level) was not patient-centered.**

4. **No sample size calculation was performed, a practice some have called unethical. This was instead conducted as a pilot study with a very small sample size and correspondingly wide confidence intervals.**

Bottom Line:

This small, pilot study found that the administration of sodium bicarbonate in prolonged OHCA without ROSC after 10 minutes of CPR in the ED was associated with a small (but statistically significant) rise in pH and bicarbonate compared to placebo, but was not associated with any improvement in survival to hospital admission or survival with good neurologic function at 1 or 6 months. Further large trials will be needed to confirm these results.