Critical Review Form
Therapy

Kim J, Kim K, Park J, Jo YH, Lee JH, Hwang JE, Ha C, Ko YS, Jung E. Sodium bicarbonate administration during ongoing resuscitation is associated with increased return of spontaneous circulation. Am J Emerg Med. 2016 Feb;34(2):225-9.

Objectives: **"to evaluate the association between the use of sodium bicarbonate and the chance of achieving return of spontaneous circulation (ROSC) [in out of hospital cardiac arrest (OHCA)]." (p. 225)**

Methods: **This single-center, observation, case-control study was conducted between January 2008 and December 2013 at a large, urban emergency department in South Korea. Patients were enrolled from a prospective OHCA registry and included adult patients (aged 18 years or older) who received CPR upon ED arrival for pulselessness. Patients with termination of CPR within 20 minutes of arrival without ROSC were excluded.**

Patients who received sodium bicarbonate in the ED were matched, 1:1, in a case-control fashion to patients who did not receive any sodium bicarbonate. This decision was made at the discretion of the treating physicians. The outcome of interest was achievement of ROSC within 20 minutes of ED presentation. The two major confounders chosen *a priori* for evaluation were initial blood bicarbonate levels and CPR duration.

A total of 771 adult patients were enrolled in the registry over the specified time period. Of these, 738 did not achieve prehospital ROSC. An additional 76 patients whose resuscitation efforts were terminated within 20 minutes of ED arrival and 63 patients who did not have a blood gas analysis before ROSC were excluded, leaving 559 total patients in the analysis. There were 331 patients (55.3%) with ROSC within 20 minutes and 268 patients (44.7%) without ROSC within the first 20 minutes. The overall median age was 68, and 62.6% were male.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	No. This was a prospective, observational study. Patients were matched in a 1:1 fashion to case and control groups. Despite this effort to balance the two groups, the study is at high risk of selection bias.

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?	N/A. Patients were not randomized.
3.	Were patients analyzed in the groups to which they were randomized?	N/A. Patients were not randomized. They were, however, analyzed based on whether or not they received sodium bicarbonate in the ED.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Uncertain. The authors provide no comparison between those patients who received bicarbonate and those who did not, either before or after case-control matching. Despite efforts to create balanced groups via multivariable logistic regression, there may still be some degree of imbalance with regards to both known and unknown confounders.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. Patients were in cardiac arrest and hence would not be aware of any treatment administered.
2.	Were clinicians aware of group allocation?	Yes. This was not a randomized trial and hence blinding was not attempted or possible. Bicarbonate administration decisions were made at the discretion of the treating physicians, and the decision to administer bicarbonate was likely, in itself, a significant prognostic indicator (selection bias).
3.	Were outcome assessors aware of group allocation?	Yes. Analysis of the data was performed without any blinding. The outcome measured (ROSC) was completely objective and hence not subject to observer bias.
4.	Was follow-up complete?	Yes. All patients had outcome data, as the outcome was whether or not they achieved ROSC in the ED.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• Prior to matching. administration of bicarbonate was associated with a decreased chance of ROSC: 22.7% vs. 54.9%, OR 0.24 (95% CI 0.17 to 0.34). ○ There was also a negative associated between cumulative dose of bicarbonate and ROSC. • After matching patients based on initial bicarbonate level and CPR duration, there was a positive association between administration of bicarbonate and ROSC, with an OR of 1.86 (95%

		CI 1.09 to 3.16). ○ There was also a positive association between cumulative bicarbonate dose and ROSC, with an OR of 1.18 (95% CI 1.04 to 1.33). • Following adjustment by multivariable logistic regression, bicarbonate remained independently associated with ROSC, with an OR of 2.49 (95% CI 1.33 to 4.65). ○ Cumulative dose likewise maintained its positive associated with ROSC with an OR of 1.27 per ampule given (95% CI 1.11 to 1.47).
2.	How precise was the estimate of the treatment effect?	See above. This was a fairly large study with relatively narrow confidence intervals.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Not entirely. The primary difference in this study is the management of OHCA. Prehospital care in this EMS system was limited to CPR, with no medications given. In our system, ACLS-level care is administered in the prehospital setting, which typically includes IV/IO medications (i.e. epinephrine) (external validity). Racial differences would not likely have had any influence on outcomes, but differences in comorbidities, frequency of bystander CPR, transport times, and availability of prehospital defibrillation may have affected the outcomes.
2.	Were all clinically important outcomes considered?	No. The only outcome in this study appears to have been ROSC within 20 minutes of ED arrival. Long-term survival and neurologic outcomes were not assessed.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This was a retrospective, observational study at high risk of selection bias despite the use of multivariable logistic regression analysis to attempt to balance the two groups being assessed. At best, this research is thought provoking but not practice changing. Additionally, the only outcome measured was ROSC within 20 minutes, which is of little clinical importance. Long-term outcomes with good neurologic function are much more patient-centered.

Limitations:

1. **This was a retrospective, observational study at high risk of selection bias despite the use of multivariable logistic regression analysis to attempt to balance the two groups being assessed.**

2. **Prehospital care in this EMS system was limited to CPR, with no medications given. In our system, ACLS-level care is administered in the prehospital setting, which typically includes IV/IO medications (i.e. epinephrine) (external validity).**

3. **No comparison of demographics and medical history between those patients who received bicarbonate and those who did not is provided, and there may still be some degree of imbalance with regards to both known and unknown confounders between the groups.**

4. **The study measured only short-term outcomes (ROSC within 20 minutes of ED arrival). The Research Working Group of the American Heart Association Emergency Cardiovascular Care Committee has recommended that large trials designed to have a major impact should use longer-term endpoints at least 90 days out coupled with some neurological and quality-of-life assessment.**

5. **The timing and reasoning behind the author's apparent decision to limit their outcome to ROSC within 20 minutes is very poorly documented.**

Bottom Line:

This retrospective, observational, case-control study found an independent association between bicarbonate administration and ROSC within 20 minutes of ED arrival, with an OR of 2.49 (95% CI 1.33 to 4.65). Despite the use of multivariable logistic regression to attempt to balance groups, this study is at high risk of selection bias. Additionally, the outcome measured is not patient-centered, and does not necessarily correlate with more important long-term outcomes that included neurologic function.