AAST Critical Care Committee Journal Review

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Title of Article
Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomized controlled, phase 3 trial.
Jaber S, Paugam C, Futier E, Lefrant J, et al. for the BICAR-ICU Study Group. Lancet.2018;392:31-40.

Link to Article
https://pubmed.ncbi.nlm.nih.gov/29910040/

Context
This article describes the BICAR-ICU trial which aimed to understand whether sodium bicarbonate infusion improves outcomes in critically ill patients with severe metabolic acidemia. Acidemia is common among patients with critical illness and associated mortality may be as high as 57%.[1] An acidotic cellular environment leads to progressive cellular dysfunction and treatment with sodium bicarbonate may be beneficial to reverse this pathophysiology. However, the effects of sodium bicarbonate infusion on hemodynamics, vasopressor requirements, and clinical outcomes have not been previously reported.[2]

Methods
- Multicenter, open-label, randomized controlled trial enrolling patients from 26 ICUs in France (2015 – 2017) with intention-to-treat analysis
- Inclusion criteria: adults age $\geq$ 18, within 48 hours of ICU admission with severe acidemia (pH $\leq$ 7.20, $PaCo_2 \leq 45$, and sodium bicarbonate concentration $\leq$ 20 mmol/L) AND with a total Sequential Organ Failure Assessment score $\geq$ 4 OR an arterial lactate concentration $\geq$ 2 mmol/L
- Exclusion criteria: respiratory acidosis, proven digestive or urinary tract loss of sodium bicarbonate, stage IV chronic kidney disease, ketoacidosis, and sodium bicarbonate infusion (including renal-replacement therapy) within 24 hours before screening
- Randomization criteria were stratified among three prespecified strata: age (cutoff 65 years), sepsis status (presence or absence), and Acute Kidney Injury Network (AKIN) score 2 or 3
- Intervention arm: hypertonic 4.2% intravenous sodium bicarbonate infusion to maintain arterial pH > 7.30 with a maximum of 1000 mL within 24 hours after inclusion
- Control arm: no sodium bicarbonate
- Primary outcome: composite of death from any cause by day 28 and the presence of at least one organ failure at day 7

Findings

- The study enrolled 389 patients with 194 patients randomized to the control group and 195 patients randomized to the bicarbonate group
- The control and sodium bicarbonate arms were well-balanced with regards to baseline characteristics and the study enrolled both medical (57%) and surgical patients (43%)
- The patients were critically ill with sepsis (61%), acute kidney injury AKIN 2 or 3 (47%), need for mechanical ventilation (83%), and need for vasopressors (80%)
- There was no difference in volume of crystalloid administered between the control and intervention arms
- The primary composite outcome of death from any cause by day 28 and the presence of at least one organ failure at day 7 occurred in 138 (71%) of 194 patients in the control group and 128 (66%) of 195 in the bicarbonate group
    - Absolute difference estimate -5.5% [95% CI -15.2% to 4.2%]; p=0.24
- Kaplan-Meier method estimate of the probability of survival at day 28 between control group and bicarbonate group was not significant
    - 46% [95% CI 40-54] versus 55% [95% CI 49-63]; p=0.09
- In the prespecified AKIN stratum of patients, the Kaplan-Meier method estimate of survival by day 28 between the control group and bicarbonate group was significant
    - 37% [95% CI 28-48] versus 54% [95% 45-65]; p=0.0283
- Metabolic alkalosis, hypernatremia, and hypocalcemia were seen more commonly in the bicarbonate group than in the control group, with no life-threatening complications reported
- Sodium bicarbonate infusion had no effect on the primary composite outcome in patients with severe metabolic acidemia, but sodium bicarbonate infusion did decrease the primary composite outcome and 28-day mortality in the stratum of patients predefined with acute kidney injury
- Bicarbonate infusion was associated with significantly decreased need for renal replacement therapy during the ICU stay

Commentary

This randomized trial showed that infusion of sodium bicarbonate for critically ill patients with acidemia pH $\leq$ 7.20 to reach pH >7.30, compared with no infusion, did not significantly decrease the primary composite outcome of mortality by day 28 or the presence of at least one organ failure at day 7 in the overall critically ill population. However, among patients with acute kidney injury at enrollment (AKIN 2 or 3), sodium bicarbonate infusion therapy did result in fewer deaths by day 28 than no infusion therapy. This mortality benefit may be related to more vasopressor-free days and more renal-replacement therapy free days for patients in the sodium bicarbonate infusion arm than for those patients in the control group. Since indication for renal-replacement therapy includes acidosis, treatment with bicarbonate would be expected to delay or limit need for renal-replacement therapy. The strengths of this study are the randomized design enrolling patients from 26 different ICUs and well-balanced baseline patient characteristics. Limitations include heterogenous etiology for metabolic acidemia (including

sepsis, hemorrhagic shock, post cardiac arrest), lack of concealment/blinding, and lack of standardization around volume of infusion of bicarbonate therapy. Furthermore, the study was under-powered because over-estimation of the effect size lead to under-estimation of the number of patients needed for the trial.

Implications for practice

BICAR-ICU provides support for use of bicarbonate infusion therapy in cases of uremic acidosis, but it is important to remember that this study does not provide evidence for use of bicarbonate in cases of purely lactic acidosis which is commonly seen in surgical populations. Lactic acidosis is treated by identification and management of the source rather than treatment with bicarbonate therapy. Patients demonstrating non anion-gap metabolic acidosis (e.g. renal tubular acidosis) are appropriately treated with bicarbonate. Similarly, those patients who have massive bicarbonate loss (e.g. digestive loss from enterocutaneous fistula) also benefit from bicarbonate replacement. The results of this trial should not, however, be extrapolated for indiscriminate use of sodium bicarbonate in all cases of critical illness and acidemia.

This study evaluated use of bicarbonate infusion at 4.2% which is not widely available or used in United States ICUs. Ampules of bicarbonate, which are commonly available in US healthcare settings, contain 50 mEq of bicarbonate in 50 mL (8.4%) and this is typically delivered as a medication push dose rather than an infusion. BICAR-ICU does not evaluate use of 8.4% sodium bicarbonate dosing nor does it evaluate isotonic bicarbonate infusion (1.3% or 150 mEq per volume 1 liter). The results of this trial cannot be used to make recommendations about use of 8.4% hypertonic or isotonic bicarbonate infusions in critically ill patients. It should be noted, however, that use of these more common concentrations of bicarbonate may be associated with side effects including hypernatremia with use of hypertonic bicarbonate, and volume overload with use of isotonic bicarbonate. Patients with cardiopulmonary complications may have a particularly adverse response to associated fluid shifts.

Finally, bicarbonate infusion is not without complications in general, and it is important to consider the metabolic consequences on surgical populations. Metabolic alkalosis and hypocalcemia were seen more commonly in the bicarbonate treatment group than in the control group of this study, but the authors reported no associated life-threatening complications. Alkalosis does, however, lead to decreased oxygen delivery and tissue perfusion which may be particularly detrimental to surgical patients as they heal from surgical interventions. Hypocalcemia may be detrimental as well, especially for patients with cardiac conditions and cardiac surgical patients. Sodium bicarbonate should not be given without careful attention to and management of these anticipated consequences.

References

1. Jung B, Rimmele T, Le Goff C, et al. Severe metabolic or mixed acidemia on intensive care unit admission: incidence, prognosis and administration of buffer therapy: a prospective, multiple-center study. Crit Care 2011; 15: R238.

2. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017; 43: 304–77.