Editorial

Sodium bicarbonate for critically ill patients with metabolic acidaemia, treatment or window dressing?

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Provenance: This is an invited Editorial commissioned by the Executive Editor Dr. Zhongheng Zhang (Department of Emergency Medicine, Sir Run-Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China).

Comment on: Jaber S, Paugam C, Futier E, *et al.* Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial. Lancet 2018;392:31-40.

Received: 11 September 2018; Accepted: 17 September 2018; Published: 29 September 2018.

doi: 10.21037/jeccm.2018.09.02

View this article at: http://dx.doi.org/10.21037/jeccm.2018.09.02

"*…It is seen how the lactic acid solution…quickly brings the ventricle to standstill…then, the alkaline solution brings back the force of the beat by its original height.*" (1).

Observations, going back to 1880, repeatedly demonstrate the deleterious effects of acidaemia on organ function. In dogs, for example, induction of metabolic acidaemia reduces ventricular function by 40% and increases pulmonary pressure (2).

In humans, severe metabolic acidaemia (blood pH ≤7.20) is associated with haemodynamic deterioration and increased mortality in critically ill patients (3). However, in these patients' effects of acidaemia are difficult to separate from effects of the organ hypoperfusion. In patients with severe ketoacidosis, transient decreases in pH to 6.8 are not associated with depressed cardiac function (4).

Even more controversy exists whether treatment of metabolic acidaemia with an alkaline solution in severely ill patients is of any benefit. Animal experiments have shown conflicting results, and also human data do not support treatment of the acidaemia (5,6).

Besides restoration of blood pH, sodium bicarbonate has some theoretical disadvantages. It may worsen intracellular acidosis, due to rapid influx of carbon dioxide. Restauration of blood pH may, perhaps counterintuitively, increase lactic acid production (7) and finally, it may decrease the concentration of ionized calcium, thereby possibly decreasing cardiac output (8).

The Surviving Sepsis Campaign recommends against treatment with bicarbonate in patients with lactic acidosis due to hypoperfusion when pH is >7.15 but does not explicate what should be done in cases with lower pH (9). In daily practice sodium bicarbonate is frequently prescribed in patients with severe acidaemia (pH <7.15) (10).

Recently, in the *Lancet*, the results of a multicenter, open-label, randomized controlled trial were published (11). Jaber *et al.* randomized 389 critically ill patients, aged >18 years, admitted to the ICU within 48 hours, with metabolic acidaemia (pH, ≤7.20; bicarbonate, ≤20 mmol/L; partial pressure of carbon dioxide, ≤45 mmHg) to treatment with 4.2% sodium bicarbonate, aimed at achieving an arterial blood pH of >7.30 during the 28-day ICU admission, or no bicarbonate infusion.

Most patients were receiving vasopressors and mechanical ventilation. Patients with ketoacidosis, already on bicarbonate treatment and stage IV chronic kidney disease were excluded. Most of the patients had sepsis. The authors identified and randomised a subgroup a priori, with renal failure, defined by at least a doubling of serum creatinine from baseline, or a urine production <0.5 mL/kg/h during 12 hours [Acute Kidney Injury Network (AKIN) stage 2–3].

The primary outcome was a composite of death by day 28 and the presence of at least one organ failure at day 7. No difference in the primary outcome was observed between the bicarbonate group and control group (66% *vs.*71%; P=0.24). However, in the 182 patients with renal

failure the primary outcome occurred less frequently in the bicarbonate group than in the control group (70% *vs.* 82%; P=0.046). Moreover, the need for renal replacement therapy during the ICU stay was lower in the bicarbonate group as compared to the control group for both the overall population (35% *vs.* 52%; P<0.0001) as well as for the patients with renal failure (51% *vs.* 73%; P=0.002). In addition, in patients with renal failure more patients in the control group were dependent on dialysis at ICU discharge (48% *vs.* 20%, P=0.047).

This trial was long overdue. Although, many reviews and expert opinions have been published data from randomized trials were lacking. This is the first randomized trial comparing treatment with sodium bicarbonate versus no treatment, in critically ill patients with severe metabolic acidaemia. Although no effect on primary outcome was found, one may speculate that some factors influenced these results.

First, carbon dioxide levels were relatively high (37, respectively 38 mmHg in both groups). This may seem "normal" but it is inadequately high considering the magnitude of acidaemia (pH 7.15 in both groups). A prerequisite for a supposed beneficial effect of sodium bicarbonate is adequate ventilation so that the carbon dioxide generated by the combination of bicarbonate and protons, can be exhaled adequately. If this is not the case, intracellular acidosis may increase, since carbon dioxide more easily penetrates cell walls compared to bicarbonate. Therefore, one may speculate that in patients with adequate ventilation, the effects of sodium bicarbonate would be more pronounced and beneficial.

Second, 24% of patients in the control group received sodium bicarbonate, as quick as 7 hours from randomisation, and 52% were on renal replacement therapy, thereby also receiving sodium bicarbonate. Furthermore, only 60% of the patients in the treatment group persistently had a blood pH >7.30. Both findings may have diluted the effects of sodium bicarbonate on the primary end point, since the primary analysis was an "intention-to-treat" analysis.

Considering its primary outcome, no need exists to change policy regarding metabolic acidaemia in severely ill patients. However, in the presence of renal failure (AKIN 2–3), the primary outcome was reached significantly less in the sodium bicarbonate group. Furthermore, mortality was significantly lower in this subgroup. How to explain this finding? Kidney dysfunction may increase the impact of an acid load by diminished filtration and impaired ammoniagenesis. However, in fact, the included patients suffered from organ hypoperfusion, and will therefore have renal failure, regardless their 'eGFR' at baseline. So maybe, defining this subgroup is merely a selection of patients with an adverse prognosis, with more benefit of treatment. Finally, the analysis comprised a subgroup, which, although being prespecified, makes it susceptible for a type I error. A randomized trial in these patients is therefore warranted.

Finally, the authors state that the need for renal-replacement therapy during the ICU stay was lower in the bicarbonate group than in the control group for both the overall population and the patients with renal failure. Problematic, however, is the fact that renal-replacement therapy was recommended in patients with persistent acidaemia. It is therefore not surprising that patients, treated with sodium bicarbonate, will less frequently reach this end point which is an effect of the treatment per se.

Summarized, in the absence of renal failure, even in patients with severe acidaemia, sodium bicarbonate administration does not influence outcome. In patients with renal failure however, sodium bicarbonate may be considered, although this finding warrants further investigation.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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doi: 10.21037/jeccm.2018.09.02
Cite this article as: Kooter AJ, Nanayakkara PW. Sodium bicarbonate for critically ill patients with metabolic acidaemia, treatment or window dressing? J Emerg Crit Care Med 2018;2:74.

