

Sodium Bicarbonate for Kidney Protection in Cardiac Surgery

Demise of Yet Another Magic Bullet?

Duminda N. Wijesundera, M.D., Ph.D., Chirag R. Parikh, M.D., Ph.D.

ACUTE kidney injury following cardiac surgery is associated with significant morbidity and mortality.¹ This important postoperative complication, termed cardiac surgery–associated acute kidney injury (CS-AKI), is multifactorial in etiology, with postulated causes including impaired renal perfusion, inflammation, ischemia–reperfusion, microemboli, oxidative stress, and nephrotoxins. Sodium bicarbonate holds theoretical promise for preventing CS-AKI, especially with respect to protecting the vulnerable renal medulla. The medulla receives a disproportionately lower share of renal blood flow (<10% of the total renal blood flow), making it an environment of relative hypoxia and acidosis, where urine first becomes acidic. Sodium bicarbonate has intrinsic natriuretic effects, in addition to its ability to alkalinize tubular fluid. It may therefore increase oxygen delivery and reduce free radical formation by neutralizing acidosis in this ischemic region of the kidney. Improving blood flow and oxygenation, as well as limiting oxidative stress by free radical formation, can help protect the medulla and, thereby, prevent kidney injury. Given this context, the publication of a pilot randomized controlled trial (RCT) in 2009 generated considerable interest.² This relatively small trial of 100 participants found that 4.0 mmol/kg of intravenous sodium bicarbonate administered as an infusion over 24 h significantly reduced rates of CS-AKI. While these initial results were promising, the report appropriately concluded that additional confirmatory trials were needed. In this issue of ANESTHESIOLOGY,



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Bailey and colleagues³ address this need in a meta-analysis of three high-quality RCTs, namely the initial 2009 trial and two subsequent larger RCTs.^{2,4,5} Instead of a traditional meta-analysis that pools the *study-level* aggregate data seen in published manuscripts, Bailey *et al.* performed an individual patient data meta-analysis that combined raw *individual-level* study data from the three included trials. This statistically more powerful approach allows for a detailed multivariable analysis of the pooled dataset, including testing for subgroup differences. Overall, the investigators found that, despite its early promise, sodium bicarbonate did not significantly reduce the risk of CS-AKI. Nonetheless, subgroup analyses suggested that it might prevent CS-AKI after elective coronary artery bypass graft (CABG) surgery, where large reductions in the risk of severe acute kidney injury were observed.

Based on these findings, what are perioperative physicians to do: simply abandon the use of sodium bicarbonate for kidney protection, or aggressively focus its use in elective CABG surgery? We would suggest that neither action is warranted. Despite the high quality of this current study, readers should weigh specific important limitations when interpreting its results. *First*, there were important imbalances in prognostically important characteristics between the study arms. Participants randomized to receive sodium bicarbonate were arguably sicker, based on a higher prevalence of insulin-dependent diabetes, peripheral arterial disease, and impaired left ventricular function. Such imbalances

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Corresponding article on page 294.

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are not surprising in smaller RCTs, as highlighted by statistical methodology research.⁶ Stated otherwise, the proportion of females, for example, is more likely to be similar across study arms if an RCT includes 1,000 participants as opposed to 50 participants. Although Bailey *et al.* showed their results to be essentially unchanged after further statistical adjustment for these baseline differences, such risk adjustment has the same limitation typically encountered in an observational study. Specifically, most statistical risk adjustment techniques (*e.g.*, multivariable regression models, propensity score methods) cannot adjust for imbalances in unmeasured participant characteristics.

Second, the large treatment effect seen in subgroup analyses should be interpreted cautiously. Given its multifactorial etiology, a 55% reduction in rates of CS-AKI after elective CABG surgery represents an implausibly large treatment effect in a subgroup consisting of only 366 participants. Furthermore, the observed subgroup differences arguably contradict the hypothetical underlying mechanisms whereby sodium bicarbonate might prevent CS-AKI. For example, longer associated cardiopulmonary bypass times during complex cardiac surgery should result in patients being exposed to more inflammation, oxidative stress, and hemolysis; nonetheless, sodium bicarbonate appeared to be less efficacious in this subgroup. Overall, these hypothesis-generating subgroup results require confirmation in a subsequent trial primarily focused on that subgroup before acceptance in clinical practice. *Third*, the authors identified an increase in postoperative mortality among patients receiving sodium bicarbonate that, while not statistically significant, was consistent across all subgroups. While this finding may have been due to imbalances in unmeasured baseline characteristics, it is important not to exclude the possibility that 4.0 to 5.1 mmol/kg of intravenous sodium bicarbonate might have unanticipated harmful effects. Unexpected adverse effects have been observed in previous trials of renal-protective agents, such as increased perioperative bleeding with high-dose *N*-acetylcysteine.⁷ In the case of sodium bicarbonate, it is possible that intracellular alkalemia or hypokalemia in vital organs, such as heart or brain, might have had harmful consequences.

Aside from a trial of sodium bicarbonate in elective CABG surgery, what other directions are needed in research on CS-AKI? At least three merit mention. Investigators should consider designing trials that evaluate a combination of potential renal-protective interventions, with each component of the combination acting on different pathophysiologic mechanisms. Combination therapy should be considered because CS-AKI is multifactorial in etiology, most single interventions inhibit one or at most a few potential pathophysiologic mechanisms, and the dominant mechanism for perioperative kidney injury in any single patient is unpredictable. In addition, as opposed to testing interventions for *preventing* CS-AKI, future studies should also focus on its early *treatment*, to thereby mitigate its harmful sequelae. Although some trials of interventions for treatment of CS-AKI have

been negative,⁸ new biomarkers for the early detection of CS-AKI may help promote further developments in this field.⁹ While serum creatinine typically takes days to increase following kidney injury, newer biomarkers such as neutrophil gelatinase-associated lipocalin are elevated sufficiently early after injury to allow for meaningful attempts at early treatment. Finally, these novel kidney injury biomarkers can also be used as endpoints in trials of interventions for preventing CS-AKI. Notably, some interventions may alleviate injury at the level of the nephron without associated changes in serum creatinine, specifically due to the presence of adequate renal reserve. The failure to recognize these episodes is being recognized as a missed opportunity in clinical trials, especially since such “subclinical” acute kidney injury is associated with long-term mortality.¹⁰

Overall, Bailey *et al.* provide a high-quality example of the benefits of collaboratively sharing trial data, and standardizing trial designs in similar clinical scenarios. While megatrials of several thousand participants are required to address many questions in perioperative medicine, such studies are often not feasible for many investigators. In the interim, we must seek to be more efficient with data collected by individual smaller trials, such that datasets can be pooled to permit statistically more powerful and comprehensive analyses. Since this approach has been adopted in only a very few perioperative studies thus far,^{11,12} there is a need for initiatives to encourage and facilitate greater uptake of this methodology. An example of such an initiative is the recently announced requirement for all RCTs published in *ANESTHESIOLOGY* to include a statement whether raw data from the study will be shared, and if so, the contact person for requesting the data.¹³ The benefits of encouraging collaborative sharing of data are clear. When performed successfully, these endeavors truly can be synergistic, resulting in a combination worth more than the sum of their parts.

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Competing Interests

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Correspondence

Address correspondence to Dr. Wijeyesundera: d.wijeyesundera@utoronto.ca.

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