

# Bicarbonate to Prevent Contrast-Induced Nephropathy in the Emergency Department: Does the Brar Study Change Recommendations?

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This is an addendum to the *Annals of Emergency Medicine* online publication “Update: Prevention of Contrast-Induced Nephropathy in the Emergency Department.”<sup>1</sup> Between the time of acceptance and publication of our updated review, an additional relevant randomized controlled trial was published by Brar et al.<sup>2</sup> The investigators enrolled consecutive patients referred for heart catheterization who were at risk for contrast-induced nephropathy, having a glomerular filtration rate less than 60 mL per minute per 1.73 m<sup>2</sup> and at least one of the following: diabetes, congestive heart failure, hypertension, or age greater than 75 years. Patients were randomized to receive either a bicarbonate or saline infusion 1 hour before contrast administration and continuing for 4 hours after the procedure. The primary outcome was a glomerular filtration rate decrease of 25% or more at any point throughout the following 4 days.

The investigators used computer-generated randomization, with proper concealment of allocation by using sealed opaque envelopes. Patients were not told their treatment assignment, but the treating physicians were aware of the intervention (unblinded). Baseline demographics and clinical characteristics were similar among the 2 groups. However, a significant proportion of patients in this cardiovascular-unit-based study were pretreated at their primary care physician’s discretion with *N*-acetylcysteine 24 hours before randomization. Aware of this potential confounding variable, the investigators stratified the randomization in blocks of 4 to evenly distribute 2 known prognostic factors: pretreatment with *N*-acetylcysteine and history of diabetes. Although the authors state that an intention-to-treat analysis was conducted, this was actually completed only for the secondary outcomes, which were added as a protocol amendment to assess 30-day and 6-month adverse events such as mortality and dialysis. For the primary outcome (glomerular filtration rate decrease >25% within 4 days of infusion), 17 patients (9.7%) randomized to the bicarbonate arm and 13 (7.3%) randomized to the saline

solution arm were excluded from the analysis for various reasons.

Although the authors conclude that, overall, bicarbonate is no more effective in preventing CIN than normal saline solution, the pooled results of this study are not applicable to the ED setting because a large proportion of the patients were pretreated 24 hours before contrast with *N*-acetylcysteine. However, the investigators do independently report the results for those patients who did not receive pretreatment with *N*-acetylcysteine. The *N*-acetylcysteine and non-*N*-acetylcysteine subgroups occurred because physicians in the Brar et al<sup>2</sup> study consciously selected, without a predefined protocol, to pretreat some of their patients with *N*-acetylcysteine. In fact, it appears from the control event rate in those selected to receive *N*-acetylcysteine (18.0%), compared with the control event rate among those who were not pretreated (11.5%), that the patients who received *N*-acetylcysteine were at higher risk for contrast-induced nephropathy than those who were randomized separately to bicarbonate or to saline solution without having received *N*-acetylcysteine the day before. It is more difficult to demonstrate an effect of an intervention in a healthier patient population than in a population with more severe disease.<sup>3</sup> The *JAMA* authors’ sample size estimate of 290 subjects was based on detecting a large, 10%, absolute risk reduction from a control event rate of 15%, ie, a 67% relative risk reduction. Therefore, it is no surprise that significant benefit or harm could not be demonstrated in a much smaller subset of patients characterized by a substantially lower risk of contrast-induced nephropathy. The risk of contrast-induced nephropathy among patients who received the bicarbonate infusion was 9.4% (8/85) compared with 11.5% (10/87) among control patients who received saline solution, yielding a relative risk of 0.82 (95% confidence interval 0.35 to 1.93). The 2 previous bicarbonate trials<sup>4,5</sup> included in the updated *Annals* evidence-based emergency medicine review<sup>1</sup> observed a larger effect of bicarbonate, with relative risks ranging from 0.12 to 0.19 and confidence intervals confined to values favoring bicarbonate over saline solution. The investigators of both of these earlier

studies stopped their data collection well before their intended sample size was reached because of apparent transitional benefit favoring bicarbonate, an action shown to frequently result in overestimation of therapeutic effect.<sup>6,7</sup>

In conclusion, the recently published study by Brar et al<sup>2</sup> may underestimate the effect of bicarbonate infusion, whereas the studies by Merten et al<sup>4</sup> and Masuda et al<sup>5</sup> probably overestimate the potential benefit because of their having been stopped early for benefit.<sup>6,7</sup> All the trials included in our review observed a benefit in favor of bicarbonate therapy, and 2 of these observations were statistically significant. Until stronger evidence is available to inform medical decisionmaking, a sodium bicarbonate infusion protocol may be considered a low-risk, low-cost prophylactic agent aimed at decreasing the risk of contrast-induced nephropathy in the emergency department setting; however, limiting exposure to contrast agents and adequate precontrast hydration are still the first line of defense.

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