

Contrasting Agendas: Science for the Bedside or Water in the Wind?

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In different ways, the 3 trials of bicarbonate infusion to prevent contrast-induced nephropathy after computed tomography (CT) scanning reviewed by Sinert et al¹⁻³ illustrate how those who designed and conducted these trials failed to meet the needs of clinicians and patients. In this editorial, we will explore the problems associated with stopping trials early and with the lack of a coherent and coordinated approach that connects the design of trials to the needs of clinical decisionmakers.

The use of contrast agents in diagnostic imaging can inflict serious iatrogenic renal injury. Most of our understanding of the prevalence and risk of contrast-induced nephropathy is derived from the coronary angiography literature that has defined it in biochemical terms as a 25% relative increase in baseline serum creatinine level or a 0.5 mg/dL (44 μ mol/L in SI units) absolute increase. Contrast-induced nephropathy affects 1% to 3% of all patients undergoing angiography⁴ but may affect as many as 20% to 30% of high-risk patients (eg, patients with renal dysfunction).⁵ Up to 30% of patients who experience contrast-induced nephropathy go on to require dialysis temporarily or permanently, and overall mortality from contrast-induced nephropathy is estimated to be 17%.⁶ This has the makings of a significant dilemma for patients requiring imaging in the emergency setting. Furthermore, this at-risk population is likely to increase as (a) the population ages with increasing prevalence of chronic kidney disease and conditions such as diabetes that predispose to contrast-induced nephropathy; (b) requests for abdominal imaging increase in emergency departments (EDs); and (c) high-resolution CT chest scanning to exclude coronary disease, thoracic aortic dissection, pulmonary embolism, or all 3 with the same test gains in popularity.

Considerable research has been aimed at the efficacy of interventions to decrease the rate of contrast-induced nephropathy in patients receiving contrast injections, and almost all trials have involved patients undergoing cardiac catheterization.¹ Are the data from the coronary angiography

literature relevant to the patients in the emergency context in which smaller volumes of intravenous contrast predominate in imaging procedures? Observational studies indicate that the incidence of contrast-induced nephropathy for all patients receiving imaging in the ED (not just those with underlying renal insufficiency) might be as high as 11%.⁷ Similarly, a retrospective Korean study of 750 patients undergoing urgent contrast-enhanced abdominal imaging reported that 3.9% of these patients demonstrated contrast-induced nephropathy and an increased mortality compared with patients who did not develop contrast-induced nephropathy.⁸ Hence, the issue of prevention of contrast-induced nephropathy in patients undergoing emergency procedures appears to be an important one, both for patients undergoing coronary angiography and for those undergoing other emergency imaging involving intravenous contrast agents.

Most trials of interventions to prevent contrast-induced nephropathy in patients undergoing coronary angiography involve extended protocols that must be initiated 24 hours or more before the procedure. This is a luxury that patients undergoing emergency procedures don't have. Appropriately, the evidence-based emergency medicine review by Sinert et al,¹ recently updated,^{2,3} limited their search and analysis of the literature to interventions provided within a 2-hour window of the patient's undergoing an imaging procedure. Among the potentially effective acute care interventions reviewed by Sinert et al,¹ sodium bicarbonate infusion appeared particularly compelling by virtue of the lack of likelihood of harm and its ease and convenience of administration as a simple adjunct to a hydration protocol that would ordinarily be administered to these same patients. Since the publication of the Sinert et al original review,¹ 2 further placebo-controlled trials of bicarbonate have been published that meet the original inclusion criteria, a protocol that could be administered on the same time scale as the emergency procedure itself.^{9,10}

The effectiveness of bicarbonate might appear promising according to the evidence-based emergency medicine review and updates¹⁻³ because 2 of the 3 trials reported a clear benefit. However, Sinert et al² point out that these same 2 trials were halted prematurely because of apparent early

benefit in dramatically reducing the incidence of chemically defined contrast-induced nephropathy.^{10,11} Although the decision to terminate these 2 trials might seem to have been taken in the interest of patient safety within a clinical trial, the deleterious effects on our understanding of contrast-induced nephropathy prevention with bicarbonate have important repercussions.

Why is stopping early because of apparent benefit an important source of bias in randomized controlled trials? The danger inherent to truncating a trial is that observed treatment effects, when assessed frequently in the course of a trial, often yield a “random high,” which, if more time were allowed to elapse, would evolve into more modest or even nonexistent benefit. In the study by Masuda et al,¹⁰ the decision to stop the trial early was unduly influenced by an inordinately high rate of contrast-induced nephropathy in the control group (34.5%), which defies all literature estimates of contrast-induced nephropathy incidence. This imbalance in risk, almost certainly the influence of chance in a small study, was more important than any marked protective benefit from bicarbonate in creating the appearance of early benefit.

Montori et al¹² identified nearly 143 randomized controlled trials that were stopped early for benefit, many of which are relevant to emergency medicine practice. Some of these studies have been subsequently shown to have demonstrated exaggerated treatment effects that were not borne out or were even contradicted by subsequent research. Frequently, trials that are halted early are presented in the media as landmark and high-profile research in which the benefits were so substantial that continuing with the trial seemed both pointless and unethical. If interim results are to be used to consider early stopping, the statistical criteria must be stringent, and the process of arriving at the decision to halt a trial for benefit must be as transparent and unbiased as possible. There is ongoing research into trial characteristics that may lead to treatment overestimations from early termination, but for now it seems prudent that if trials need to be stopped at all, they should be stopped only after trends are confirmed, which may require the accumulation of many events in the trial, perhaps as many as 400. The total accumulated number of contrast-induced nephropathy events observed in the 2 trials stopped early was 21, the 2 trials having been stopped after only 9 and 12 events, respectively.^{10,11}

Who benefits from early termination? There were no corporate interests at play when these 2 studies were terminated. Arguably, the ethics of stopping a study early because of apparent benefit are questionable when one considers the greater ethical implications and the larger harm associated with promulgating a treatment benefit that might not even exist or at the very least is far more modest than is suggested by the degree of benefit present at study termination.¹³

Compounding the uncertainty created by the fact that 2 successive trials of bicarbonate were stopped early, the trial by Brar et al,⁹ which was also ostensibly designed to address contrast-induced nephropathy prevention through use of an acute treatment protocol with bicarbonate, is hampered by nearly half of enrolled patients receiving *N*-acetylcysteine in the 24 hours before undergoing angiography, resulting in yet another underpowered study in which the patients receiving the emergency intervention only may have been at less risk of contrast-induced nephropathy and hence less likely to benefit from preventive intervention.

So there is a troubling disconnection between the current evidence base as it relates to the prevention of contrast-induced nephropathy for patients requiring emergency imaging and the needs of clinicians trying to protect patients from this potentially lethal complication. Be it the paucity of studies that adequately inform our understanding of acute prevention protocols or relevant trials being stopped early for benefit, one gets the impression that key decisions in study design and execution were being dominated by issues that, in hindsight at least, have more traction with researchers than with clinical decisionmakers. Similarly, there have been no coordinated efforts to study contrast-induced nephropathy prevention in acutely ill patients undergoing emergency imaging with intravenous contrast, even though the burden of illness from contrast-induced nephropathy might actually derive largely from that context and may increase over time.

The Canadian Institutes of Health Research has recognized that the failure of the research enterprise to consult with and obtain buy-in from end users when designing and executing studies is a widespread problem that ultimately threatens the production of relevant research or prevents the uptake of evidence into practice. In response to these concerns, the Canadian Institutes of Health Research has promulgated programs in “integrated knowledge translation.”¹⁴

The term *integrated knowledge translation* describes an approach (and a grant funding structure) in which researchers and research users (clinicians) work together to shape the entire research process, starting with collaboration on setting the research questions and extending to interpreting the findings and helping disseminate the research results. This multistakeholder method of planning and executing clinical research should produce findings that are more likely to be relevant to, and used by, the research end users.¹⁵ This novel focus on “real-world” effectiveness over efficacy is the hallmark of the shift in research orientation toward comparative effectiveness and pragmatic clinical trials.^{16,17}

The current situation, as well as many analogous situations, calls for coordinated efforts, ie, adequately powered trials designed with input from clinicians. Our wish list for such trials would be that they enroll ED patients, test regimens that make sense in the acute setting, and, whenever

possible, directly measure their effect on patient-important outcomes. When and if one such trial of bicarbonate to prevent contrast-induced nephropathy comes to be, let's make sure that it doesn't get halted prematurely because of an interim analysis suggesting early benefit from the intervention strategy.

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