

EDITORIAL COMMENT

High Urine Output With Matched Hydration for CI-AKI Prevention

“Salus Per Aquam” (Health Through Water)*

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Contrast-induced acute kidney injury (CI-AKI) is one of the leading causes of hospital-acquired acute renal insufficiency, occurring in approximately 12% of patients undergoing percutaneous coronary intervention (PCI). This complication is associated with strikingly higher in-hospital and long-term morbidity and mortality, persistent loss of kidney function, and risk of progression to end-stage renal disease. Pre-existing chronic kidney disease (CKD), advanced age, diabetes, and urgent and emergency PCI increase the risk of CI-AKI up to 30% as compared with a 2% rate in the general population. Because CI-AKI is predictable in most cases, preventive strategies are the only effective therapeutic approach. Accordingly, several studies have been focusing on prevention, most often with pharmacological agents. However, none of the tested drugs showed irrefutable positive effects, particularly in patients with severe CKD. Exceptions to rather disappointing results are limiting contrast dosages and adequate intravenous pre-procedural hydration. The beneficial effects of isotonic saline infusion have been demonstrated in low-risk patients with normal renal function, but they were not substantiated beyond question in those with CKD. Current guidelines recommend isotonic saline at an infusion rate of 1.0 ml/kg/h or less (0.5 ml/kg/h) in the case of left ventricular ejection fraction (LVEF) <35% or New York Heart Association functional class >2 (1).

However, the recommended hydration rate represents a “safe” regimen conceived to avoid fluid overload and pulmonary edema, rather than to achieve a “true” hydration. Thus, despite general agreement on its benefit, most patients do not receive sufficient hydration before contrast exposure. In particular, patients at high risk due to severe LVEF depression and/or advanced CKD, who may benefit most from a vigorous hydration, receive less fluid volume than those without cardiac and renal dysfunction. Indeed, heavy systemic hydration in these patients is poorly tolerated and potentially harmful. Interestingly, whereas hydration remains the cornerstone for CI-AKI prevention, a randomized controlled trial comparing a strategy of volume expansion to no volume expansion has not been performed to date.

Another still controversial issue is the association of hydration with diuretics. Current guidelines recommend discontinuing diuretic agents, despite their potential renal protective effects. Indeed, furosemide inhibits sodium-potassium-chloride cotransport in the thick ascending limb of the Henle loop. This nephron segment is at the greatest risk of ischemic injury due to high metabolic demand and low oxygen delivery. Notwithstanding the postulated benefits (reduction of renal oxygen consumption and increased urine flow leading to contrast dilution and reduced direct toxicity on renal tubules), clinical studies demonstrated that furosemide is associated with increased CI-AKI incidence, likely due to intravascular volume depletion.

Interestingly, the PRINCE (Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation) study showed that forced diuresis, achieved with a single diuretic dose in combination with intravenous fluid replacement matched to urine output, provided a modest protective effect against CI-AKI (2). This study demonstrated an inverse correlation

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between urine flow rate and creatinine increase after contrast exposure, with a significantly lower risk of CI-AKI and dialysis when patients achieved a mean urine flow rate >150 ml/h. These results support the concept that high urine output is required to protect the kidney. On this premise, a strategy able to maintain the positive effects of furosemide-induced high-volume diuresis and, at the same time, to preserve intravascular volume (euvolemia) through simultaneous matched hydration should prevent CI-AKI in high-risk patients.

The RenalGuard system (RenalGuard Solutions, Milford, Massachusetts) has been developed in order to achieve real-time, automated fluid matching by continuously measuring urine output—accelerated by a bolus of intravenous furosemide—and replacing it with an exactly matched amount of infused fluid volume. The system comprises a urinary collection bag connected to a Foley catheter and hung on a digital scale that drives a high-volume fluid pump. Any amount of urine entering the collection bag results in an equal volume of saline infused intravenously back to the patient. The infusion rate is adjusted milliliter for milliliter and second by second in response to changes in urine output, thus preventing net fluid loss and fluid overload. By administering a small bolus (250 ml) of fluid initially and stimulating diuresis with furosemide (0.25 to 0.5 mg/kg), urine output increases to >300 ml/min in about 60 min, and this rate is maintained during the interventional procedure and for the following 4 h.

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The results of the study published in this issue of *JACC: Cardiovascular Interventions* (3) represent an important piece of evidence by which to guide the contemporary management of patients who are at high risk of CI-AKI and undergo contrast-enhanced procedures. Of note, this is the first systematic review and meta-analysis of the published randomized trials that assessed the effect of the RenalGuard system in patients undergoing coronary procedures (diagnostic and interventional) and transcatheter aortic valve replacement (TAVR). Undoubtedly, the meta-analysis was well conducted using the PRISMA guidelines. Four randomized trials, including 698 patients, were selected following the PICOS criteria. The RenalGuard therapy was associated with a significant reduction of CI-AKI (7.76% vs. 21.43%; $p < 0.00001$), a lower need for renal replacement therapy (0.58% vs. 3.45%; $p = 0.02$), and a nonsignificant lower rate of mortality, post-procedural acute coronary syndrome, stroke, and acute pulmonary edema. Of note, most of the patients treated with the

RenalGuard reached high urine output despite severely depressed kidney function without clinically significant changes in electrolyte balance and hemodynamic or systemic adverse reactions. Although well standardized and codified with the assistance of a dedicated software, this meta-analysis may have the common limitations of several previous meta-analyses. Namely, it was on the basis of the overall study populations and not on patient-level data. Another limitation is the fact that the analyzed studies were not powered to detect differences in clinical outcome, they did not provide data on the cost-benefit ratio, and long-term (1-year) impact of the RenalGuard therapy was reported by 1 trial only (4). Nevertheless, the considerable magnitude of the between-group differences in CI-AKI incidence and the uniform positive results among all trials suggest that it is quite unlikely that this is a faulty meta-analysis with a significantly incorrect assessment of the RenalGuard treatment effect.

A pivotal trial (Evaluation of RenalGuard System to Reduce the Incidence of Contrast Induced Nephropathy in At-Risk Patients [CIN-RG]; [NCT01456013](#)) involving up to 20 U.S. sites is in progress. The trial is comparing RenalGuard plus N-acetylcysteine versus saline (3 ml/kg bolus, 1.5 ml/kg during and 4 h after angiography) plus N-acetylcysteine. The trial, whose results are awaited with interest, has already randomized 236 of 430 planned patients who are at high risk of CI-AKI (estimated glomerular filtration rate [eGFR] 15 to 45 ml/min or 46 to 60 ml/min in case of 2 additional risk factors) and scheduled to receive ≥ 75 ml of contrast. The primary efficacy endpoint is CI-AKI occurrence, whereas secondary endpoints include 90-day mortality, myocardial infarction, stroke, heart failure, and dialysis. Another randomized, sham-controlled trial (REDUCE-AKI [The Effect of the Forced Diuresis With Matched Hydration in Reducing Acute Kidney Injury During TAVI]; [NCT01866800](#)) is currently conducted in Israel to examine the effect of RenalGuard for CIN-AKI prevention in patients undergoing TAVR (5). Patients are randomized in a 1:1 fashion to the RenalGuard system (active group) versus nonmatched saline infusion (sham-controlled group). Moreover, in a recent investigator-driven, single-center, retrospective analysis of prospectively collected data, the RenalGuard therapy resulted in lower CI-AKI incidence and, unexpectedly, in significant eGFR improvement in high-risk patients undergoing coronary angiography, PCI, or TAVR (6). This may suggest that, besides the supposed beneficial effects of the RenalGuard (faster transit through the tubules, decreased luminal concentration, and reduction in sludging and precipitation of the

contrast), other mechanisms may play a role and should be further investigated. In this regard, some insights can be inferred from the data of the MYTHOS (Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention) trial (7). This trial indicates that RenalGuard-treated patients achieve a significantly higher volume of renal-targeted hydration (4,000 ml vs. 1,750 ml) in a much shorter time (6 h vs. 24 h) than those treated with standard systemic hydration, markedly amplifying the kidney protective effects of hydration.

In conclusion, despite the limitations that are common to all meta-analyses and the small

number of trials published, the authors must be complimented for this important study. The results of their meta-analysis, along with those of other multicenter randomized trials that are needed to corroborate the present findings, suggest that furosemide-induced high-volume diuresis and maintenance of euvoemia through matched fluid replacement (RenalGuard therapy) might become a standard of care strategy for the prevention of CI-AKI in high-risk patients.

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