JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 5, NO. 4, 2012

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.

LETTERS TO THE EDITOR

More Positive Fluid Balance Could Explain Lower Risk of Contrast Nephropathy

The paper by Marenzi et al. (1) in *JACC: Cardiovascular Interventions* on prevention of contrast-induced nephropathy (CIN) using furosemide with matched hydration deals with a pertinent and pervasive problem. In this randomized trial of 170 patients who received contrast media during coronary procedures, the investigators compared standard-of-care hydration using intravenous (IV) isotonic saline with furosemide-forced diuresis and IV isotonic saline infusion matched to the urine output. This intervention arm was associated with a lower incidence of CIN (4.6% vs. 18% in control subjects, $p = 0.005$). However, a crucial piece of data missing in the study, which might confound the results, is the patients' net fluid balance at the end of their respective protocols. Adequate hydration before contrast administration is considered the cornerstone of CIN prevention, although no randomized controlled trial has studied the benefit of hydration alone. It would have added to the validity of the study had the patients' weights been mentioned before and after the protocol because that could be a good surrogate of the patients' net hydration status. Estimation of the net fluid balance based just on the difference between the cumulative IV hydration and the urine outputs shows that patients in the furosemide-matched hydration group were perhaps much better volume repleted than the control subjects were. Patients in the intervention arm received cumulative IV saline volume of 3,995 ± 1,401 ml, with infusion rates matched to the urine output (minus the initial 250-ml IV saline bolus). This indicates an even-to-slightly-positive net fluid balance over the duration of the protocol. The control group, however, received a cumulative IV saline volume of 1,742 ± 290 ml while putting out a urine volume of 3,117 ± 876 ml. This clearly suggests a net negative fluid balance of about 1.3 l. Hence, how much of the final efficacy of furosemide-matched hydration protocol over standard saline hydration in preventing CIN could be attributed to the use of furosemide, versus to the fact that patients in the intervention arm just happened to be much better hydrated, remains debatable. Some of the classic studies that studied volume repletion as a measure to prevent CIN have shown that patients who did better tended to be in an even-to-positive fluid balance, although the results were not always statistically significant (2,3)

The study, however, definitely forces us to question our purported definition of "adequate" isotonic saline hydration in preparation for contrast administration (1.0 to 1.5 ml/kg/h for 3 to 12 h before the procedure and continuing for 6 to 24 h after the procedure, per current guidelines) (4). The control group clearly received hydration that was commensurate with guidelines, yet did significantly worse than the intervention "superhydrated" arm. This could be a novel proof of concept, worth validating by future trials, wherein an isotonic saline hydration rate of as much as 600 ml/h for a shorter duration of about 6 h (as was used in the study) might be a better prophylactic regimen against CIN compared with what current guidelines recommend. A shorter hydration regimen might also be logistically easier to implement and have implications for cost savings.

***Veeraish Chauhan, MD**

*Division of Nephrology
Department of Medicine
Drexel University College of Medicine and Hahnemann University Hospital
245 North 15th Street
Mail Stop 437
Philadelphia, Pennsylvania 19102
E-mail: veeraish.chauhan@drexelmed.edu

doi:10.1016/j.jcin.2012.02.004

REFERENCES

1. Marenzi G, Ferrari C, Marana I, et al. Prevention of contrast nephropathy by furosemide with matched hydration: the MYTHOS (Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention) trial. J Am Coll Cardiol Intv 2012;5:90–7.
2. Trivedi HS, Moore H, Nasr S, et al. A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. Nephron Clin Pract 2003;93:C29–34.
3. Bader BD, Berger ED, Heede MB, et al. What is the best hydration regimen to prevent contrast media-induced nephrotoxicity? Clin Nephrol 2004;62:1–7.
4. Levine GN, Bates ER, Blankenship JC, et al. ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;2011:e44–122.

Hydration Is Critical for Prevention of Contrast-Induced Nephropathy

Marenzi et al. (1) recently reported the results on a single-center, prospective, randomized, nonblinded trial to investigate the role of combined furosemide-induced high-volume diuresis and automated matched hydration (intervention group), combined with standard saline hydration (control group), for the prevention of contrast-induced nephropathy (CIN) in chronic kidney disease patients undergoing coronary procedures.

However, it is worth noting that the 2 study groups were different with respect to the fluids infused. In the intervention group during the 6 ± 1 h of treatment, the volume of saline hydration was 3,995 ± 1,401 ml. Urine output was matched to the infusion rate (minus the 250-ml fluid bolus received as specified in the protocol). The intervention group thus had a net positive fluid

balance. In the control group, during the 25 ± 2-h treatment period, the cumulative saline hydration was 1,742 ± 290 ml. Importantly, however, urine output during hydration in the control group was 3,117 ± 876 ml. Thus, the control group had a net negative fluid balance. The reason for this finding is not entirely clear. It is possible that continuing the diuretics that both groups of patients were on as outpatients caused this finding. Forty-eight of 83 (58%) of patients in the control group were on diuretics, and there was no protocol to stop these medications before the intervention. Thus, the differences in the fluid administered and the fluid balance achieved likely influenced the results of the study in the 2 groups.

Majumdar et al. (2) in their meta-analysis comparing furosemide-based intervention with saline hydration for the prevention of CIN concluded furosemide-based interventions to be detrimental to saline hydration for the prevention of CIN. However, the studies that were analyzed did not have as rigorous a method of hydration in the intervention arms as did the study by Marenzi et al. (1).

In light of prior randomized controlled trials, to demonstrate benefit of furosemide-based intervention with hydration over saline hydration alone for the prevention of CIN, it is critical to keep both study arms equally hydrated. Failure to do so may influence the results of the study. Thus, studies maintaining equal hydration in both groups are needed to demonstrate a difference in outcome due to the intervention.

***Deep Sharma, MD**

*Department of Nephrology
Albert Einstein College of Medicine/
Montefiore Medical Center
Ullmann Building Room 615
1300 Morris Park Avenue
Bronx, New York 10461
E-mail: dsharma@montefiore.org

doi:10.1016/j.jcin.2012.02.007

REFERENCES

1. Marenzi G, Ferrari C, Marana I, et al. Prevention of contrast nephropathy by furosemide with matched hydration: the MYTHOS (Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention) trial. J Am Coll Cardiol Intv 2012;5:90–7.
2. Majumdar SR, Kjellstrand CM, Tymchak WJ, Hervas-Malo M, Taylor DA, Teo KK. Forced euvolemic diuresis with mannitol and furosemide for prevention of contrast-induced nephropathy in patients with CKD undergoing coronary angiography: a randomized controlled trial. Am J Kidney Dis 2009;54:602–9.

Reply

We appreciate the thoughtful comments of Drs. Chauhan and Sharma on our study. We agree with them with regard to the critical importance of generous hydration and positive fluid balance for contrast-induced nephropathy prevention. Current guidelines recommend administration of isotonic electrolyte solutions at an infusion rate of 1.0 ml/kg/h or less (0.5 ml/kg/h) in case of left ventricular ejection fraction <35% or New York Heart Association functional class >2 (1). We believe that this hydration rate represents a "safe" regimen conceived for avoiding fluid overload and pulmonary edema rather than an "effective" patient hydration. Indeed, a 70-ml/h hydration rate for 24 h in a 70 kg fasting patient is the minimal fluid volume needed to avoid dehydration. By contrast, vigorous hydration before coronary procedures is difficult logistically and poorly tolerated, in particular in the presence of impaired cardiac and renal function. Thus, despite general agreement on hydration benefit and strong recommendation of all guidelines, most patients are not sufficiently hydrated in routine clinical practice.

In our study (2), saline infusion and urine output were rigorously measured. However, from these data it is not possible to extrapolate the net fluid balance, because all patients were encouraged to freely drink water after coronary angiography. Thus, it is likely that the control group too had a modestly positive or, at worst, a slightly negative fluid balance.

Although further studies are needed to elucidate the mechanisms of the innovative preventive treatment described in our report, it is unlikely that its beneficial effects might be explained by the initial 250-ml saline bolus only. We believe that simultaneous high urine-flow rate resulting from furosemide administration together with dehydration prevention obtained by exactly matching saline infusion might have played an important role in the results observed in the treated patients. Indeed, preclinical studies demonstrated that prolonged contact time of contrast with the tubular epithelial cells is associated with a greater tubular damage, as indicated by biomarkers (3), and that high urine-flow rates flush the renal tubules and lower contrast concentration in tubular fluid. This accelerates contrast excretion, thus reducing the exposure time of tubular cells. Therefore, the high urine-flow rate achievable with this innovative treatment might lower contrast concentration and viscosity and accelerate contrast excretion, thus reducing the exposure time of tubular cells to its toxicity (4).

***Giancarlo Marenzi, MD**
Cristina Ferrari, MD
Antonio L. Bartorelli, MD

*Centro Cardiologico Monzino
Via Parea 4
20138 Milan
Italy
E-mail: giancarlo.marenzi@ccfm.it

doi:10.1016/j.jcin.2012.03.001

REFERENCES

1. Wijns W, Kolh P, Danchin N, et al., for the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI). Guidelines on myocardial revascularization. Eur Heart J 2010;31:2501–55.
2. Marenzi G, Ferrari C, Marana I, et al. Prevention of contrast nephropathy by furosemide with matched hydration: the MYTHOS (Induced Diuresis With Matched Hydration Compared to Standard Hydration