

Prevention of Contrast-Induced Nephropathy with Volume Expansion

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Background and objectives: Contrast-induced nephropathy is one of the few preventable forms of acute kidney injury. Several pharmacologic agents have been evaluated for the prevention of contrast-induced nephropathy, yet disappointingly, few have been shown conclusively to reduce the risk for this condition. A series of studies have demonstrated that volume expansion, particularly with intravenous fluids, is an effective intervention to reduce the risk for contrast-induced nephropathy.

Design, setting, participants, & measurements: This article reviews the clinical trials that have assessed the role of volume expansion for the prevention of contrast-induced nephropathy.

Results: The administration of isotonic sodium chloride before and after radiocontrast injection seems to be more protective than equivalent volumes of hypotonic saline and, when feasible, should be administered over a sustained period of time. Recent clinical trials suggested that an abbreviated regimen of intravenous sodium bicarbonate may be superior to a comparable protocol of sodium chloride. Although a small number of studies have found that volume supplementation by mouth may be effective in preventing contrast-induced nephropathy, the routine use of enteral fluids or solute in lieu of intravenous fluids in high-risk patients cannot be recommended at this time. Rather, liberal oral fluid and solute intake should complement intravenous fluid administration to minimize risk.

Conclusions: Future studies will be required to define clearly the optimal prophylactic intravenous fluid regimen for contrast-induced nephropathy and further delineate the independent role of oral volume expansion for the prevention of this condition.

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Intravascular administration of iodinated radiocontrast media remains a common cause of acute kidney injury (AKI) and is associated with prolonged hospital stay, increased health resource use, and in-hospital mortality (1–4). Contrast-induced nephropathy (CIN) is unique in that its risk factors are widely known, it is universally iatrogenic, and its timing is highly predictable. These factors make CIN one of the few avoidable forms of AKI and a condition for which a standardized preventive strategy would be feasible and effective. Several different pharmacologic interventions have been evaluated for the prevention of CIN (5–9). Unfortunately, few have been found to be beneficial. The principal intervention that has demonstrated efficacy in reducing the risk for CIN in multiple studies is extracellular volume expansion, primarily with the administration of intravenous fluid (10–13). With the increasing recognition in the past two decades that intravenous volume supplementation effectively reduces the risk for CIN, several studies have aimed to define the optimal fluid composition, rate, timing, and duration of therapy. The follow-

ing review describes our current understanding of the role of volume expansion in the prevention of CIN and highlights the salient findings of those studies that have shaped the current evidence basis for this prophylactic therapy.

Pathophysiology of CIN and the Potentially Attenuating Effects of Volume Expansion

The precise pathophysiologic mechanism by which iodinated radiocontrast precipitates kidney injury remains a matter of ongoing investigation. Multiple pathogenic mechanisms have been implicated in the development of CIN; principal among them are altered renal hemodynamics contributing to medullary hypoxia and direct cytotoxicity of radiocontrast (14–16). It therefore seems plausible that extracellular volume expansion at the time of radiocontrast administration may serve to counteract these two processes. Neurohumoral effects of volume expansion that may attenuate radiocontrast-induced medullary hypoxia include suppression of vasopressin as well as inhibition of the renin-angiotensin axis; increased synthesis of vasodilatory renal prostaglandins may also play a role (17–21). It is interesting that recent studies using blood oxygenation level-dependent MRI demonstrated that water diuresis improves medullary oxygenation. Although these studies were based on water administration, which has not been shown to be an

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effective preventive strategy for CIN in clinical practice, the results suggest that volume expansion may in fact act by counterbalancing the ischemic effect of radiocontrast on medullary tubular cells (22–24). Iodinated radiocontrast has also been shown to have direct cytotoxic effects on tubular cells. Dilution of the contrast medium, particularly in the medullary tubular segments, may counteract this effect and reduce direct cellular damage. Likewise, an effect of radiocontrast to increase tubular fluid viscosity may be diminished by intravascular volume expansion (25). It is important to note that these potentially attenuating effects of volume expansion are speculative, and the precise mechanism by which volume expansion protects against CIN remains unknown.

Animal Studies

Studies in animal models have demonstrated that volume depletion accentuates the hemodynamic effects of radiocontrast on the kidney. More than two decades ago, Larson *et al.* (26) compared the magnitude and duration of vasoconstriction after radiocontrast injection in a group of sodium-deplete and sodium-replete dogs. Compared with sodium-replete dogs, the reduction in renal blood flow was more pronounced (42.2 *versus* 12.2%) and of greater duration (343 *versus* 147 s; $P < 0.01$) in sodium-deplete dogs.

Yoshioka *et al.* (27) later assessed changes in GFR in water-deprived and non-water-deprived rats that were administered radiocontrast as well as in water-deprived rats that received only saline. A reduced GFR was observed 24 h after radiocontrast administration in water-deprived rats, and this effect persisted at 72 h. In contrast, non-water-deprived rats that were given radiocontrast and water-deprived rats that were administered saline demonstrated no reduction in GFR.

Last, Erley *et al.* (28) examined the effect of radiocontrast on GFR in rats, including a group that was administered NG-nitro-L-arginine methyl ester (L-NAME) to induce a hypertensive, nitric oxide-depleted state. Among volume-depleted L-NAME rats, radiocontrast induced a drop in GFR (1.25 to 0.89 ml/min; $P < 0.05$). This effect was much less pronounced in volume-depleted rats that were not treated with L-NAME and was not present in volume-expanded L-NAME rats, underscoring the increased vulnerability of the volume-depleted, “at risk” kidney to the effects of radiocontrast. These three studies helped to establish that volume depletion compounds the nephrotoxicity of radiocontrast, an observation that provided the foundation for studies that investigate the protective effects of volume expansion.

Observational Human Studies

Early data on the benefit of volume supplementation stem from observational studies. In 1981, Eisenberg *et al.* (29) conducted a single-arm observational study to assess the incidence of CIN in a cohort of 537 patients who received intravascular volume expansion at the time of angiography. Patients received an average of 550 ml of 0.9% NaCl during each hour of the procedure. None of the patients developed CIN compared with 12% of patients in a historic cohort who had received 80 ml/h 5% dextrose in water, leading the investigators to conclude that

volume expansion of the intravascular space reduces the incidence of CIN (30). The major limitation to this study was that differences in clinical risk factors for CIN between study patients and historic control subjects were not reported.

A subsequent single-arm study by Kerstein *et al.* (31) enrolled 150 patients who were undergoing noncoronary angiography and received 0.5% NaCl in 5% dextrose at a rate of 1 to 3 ml/kg per h for 8 h before and 6 h after the procedure. Among 31 study patients with underlying renal dysfunction, an additional 300 to 500 ml of intravenous fluid and 20 to 40 mg of furosemide were administered before the procedure. None of the patients demonstrated CIN. The investigators hypothesized that volume expansion may have explained this observation; however, this study had no matched control group with which the effect of intravenous fluids was compared, and most patients had no evidence of preexisting renal insufficiency, suggesting that the overall risk for CIN in this study population was fairly low. Nonetheless, these two studies provided early insights into the potential prophylactic effect of volume expansion on the development of CIN.

Clinical Trials of Intravenous Fluids

A series of randomized clinical trials that were performed in the past 15 yr forms much of the current evidence basis on the role of intravenous fluid supplementation for the prevention of CIN and provides preliminary data on the impact of intravenous fluid composition, rate, and duration of administration. These studies, which we identified by searching Medline for clinical trials on intravenous fluids and CIN and by reviewing any salient references, are depicted in Table 1.

In 1994, Solomon *et al.* (10) reported the results of a clinical trial on the prophylactic effects of intravenous fluid alone or in combination with intravenous mannitol or furosemide. Patients who were undergoing coronary angiography with a serum creatinine (SCr) >1.6 mg/dl or an estimated creatinine clearance <60 ml/min were randomly assigned to receive 0.45% NaCl at a rate of 1 ml/kg per h for 12 h before and 12 h after angiography or this same intravenous fluid regimen along with either 25 g of intravenous mannitol or 80 mg of intravenous furosemide before angiography. Among the 28 patients who received intravenous fluid alone, three (11%) developed CIN, compared with 7 (28%) of 25 in the mannitol group and 10 (40%) of 25 who received furosemide in addition to intravenous fluids ($P = 0.02$ for comparison with intravenous fluid alone; Figure 1). Postprocedure urine volume and sodium excretion as well as changes in body weight were comparable among the groups. This trial provided important evidence that hypotonic fluids alone are more protective than hypotonic fluids supplemented with mannitol or furosemide; however, this trial did not establish that intravenous fluids are superior to oral fluids or to no intravenous fluids. Moreover, the number of patients in each study group and the overall sample size were small. Nonetheless, these findings helped to establish the administration of 0.45% NaCl intravenously as a preventive strategy in high-risk patients, provided preliminary data on a target duration and rate of intravenous fluid therapy, and helped to con-

Table 1. Randomized trials of intravenous fluids^a

Study	No. of Patients	Intravenous Fluid Comparison	Intravenous Fluid Rate	Intravenous Fluid Duration	Baseline SCR	Rates of CIN	P
Solomon <i>et al.</i> (10)	78	0.45% NaCl ^b	1 ml/kg per h	12 h before and 12 h after	2.1 mg/dl	11 <i>versus</i> 25 <i>versus</i> 40% ^c	<0.05
Mueller <i>et al.</i> (12)	1383	0.45% NaCl <i>versus</i> 0.9% NaCl	1 ml/kg per h	Before and 12 h after	0.9 mg/dl	2.0 <i>versus</i> 0.7%	0.04
Krasuski <i>et al.</i> (33)	63	0.45% NaCl <i>versus</i> 0.9% NaCl	–	0.45% NaCl: 1 ml/kg per h 12 h before and after 250 ml 0.9% NaCl 20 min before and 1 ml/kg per h 0.45% NaCl 12 h after	1.8 to 1.9 mg/dl	10.8 <i>versus</i> 0.0%	0.136
Bader <i>et al.</i> (34)	39	0.9% NaCl (both groups)	–	300 ml once <i>versus</i> 2000 ml over 24 h	0.9 mg/dl	15.0 <i>versus</i> 5.3%	0.605
Merten <i>et al.</i> (11)	119	NaHCO ₃ <i>versus</i> NaCl	3 ml/kg per h before and 1 ml/kg per h after	1 h before and 6 h after	1.71 to 1.89 mg/dl	13.6 <i>versus</i> 1.7%	0.02
Briguori <i>et al.</i> (35)	326	NaHCO ₃ <i>versus</i> NaCl	NaHCO ₃ : 3 ml/kg per h before and 1 ml/kg per h after NaCl: 1 ml/kg per h	NaHCO ₃ : 1 h before and 6 h after NaCl: 12 h before and 12 h after	1.93 to 2.04 mg/dl	1.9 <i>versus</i> 9.9% ^d	0.019 ^d
Recio-Mayoral <i>et al.</i> (36)	111	NaHCO ₃ <i>versus</i> NaCl	NaHCO ₃ : 5 ml/kg per h before and 1.5 ml/kg per h after NaCl: 1 ml/kg per h after	NaHCO ₃ : 1 h before and 12 h after NaCl: 12 h after	1.0 mg/dl	1.8 <i>versus</i> 21.8%	<0.001

^aStudies are not rated for quality. CIN, contrast-induced nephropathy; SCR, serum creatinine.

^b0.45% NaCl *versus* 0.45% NaCl + intravenous mannitol *versus* 0.45% NaCl + intravenous furosemide.

^cSaline *versus* saline/mannitol *versus* saline/furosemide, respectively.

^dDenotes comparison of NaHCO₃/N-acetylcysteine (NAC) *versus* NaCl/NAC.

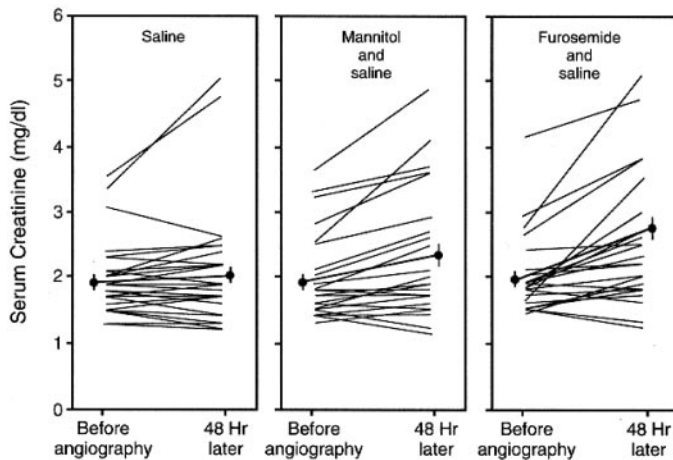


Figure 1. Serum creatinine (SCr) concentrations immediately before the administration of radiocontrast agent (after 12 h of hydration) and 48 h later in patients with chronic renal insufficiency. The mean (\pm SE) for each treatment group is indicated by the heavy lines and circles. The increase in SCr was significantly greater in the furosemide group than in the saline group ($P < 0.01$ by t test). Reprinted from reference (10), with permission.

firm that the administration of mannitol and furosemide was not beneficial.

There have been more recent studies of the effect of intravenous fluid combined with furosemide and mannitol. Stevens *et al.* (32) randomly assigned 98 patients who had chronic kidney disease (CKD) and were undergoing elective coronary angiography to receive either forced diuresis with intravenous crystalloid, furosemide, and dopamine along with intravenous mannitol if the pulmonary capillary wedge pressure was <20 mmHg or intravenous crystalloid with placebos. There were no differences in the mean change in SCr or in the rate of CIN based on six different definitions. Patients who had postprocedure urine flow rates >150 ml/h demonstrated a lower rate of CIN than those with urine flow rates <150 ml/h (21.6 versus 45.9%; $P = 0.03$); however, this finding does not confirm that higher rates of urine output are protective but rather may reflect the impact of contrast-induced injury on maximal urine production. The protective effect of achieving high postradiocontrast urine flow rates will require further study before a preventive strategy of forced diuresis can be advocated.

Until 2002, little was known about the effect of fluid tonicity on the incidence of CIN. Mueller *et al.* (12) addressed this question by randomly assigning patients who were undergoing elective or emergent coronary angioplasty to periprocedural intravenous volume expansion with either 0.45% NaCl or 0.9% NaCl. The overall rate of CIN was greater in patients who received half-isotonic saline compared with those who were administered isotonic saline (2.0 versus 0.7%; $P = 0.04$), whereas vascular complications, need for dialysis, length of hospital stay, and mortality rates were comparable in the two groups. The very low incidence of CIN in this study was likely related to the normal baseline level of renal function among most

patients (mean SCr 0.92 to 0.93 mg/dl) and the small proportion of patients with underlying diabetes (16%). Isotonic saline was associated with lower rates of CIN than hypotonic saline in women (0.6 versus 5.1%; $P = 0.01$) and those with diabetes (0.0 versus 5.5%; $P = 0.01$), yet among patients with baseline SCr levels above the normal range as well as those with SCr >1.6 mg/dl, there were no statistically significant differences in the rate of CIN; however, the small number of patients within these subgroups substantially limited the power of these comparisons. Despite these limitations, this study suggested that isotonic saline is more protective against CIN than hypotonic saline.

In 2003, Krasuski *et al.* (33) published the results of a randomized trial that examined the effect of duration of intravenous fluid therapy on CIN. Patients who had preexisting CKD and were undergoing elective coronary angiography were randomly assigned to receive either 250 ml of 0.9% NaCl intravenously over 20 min on call to the procedure or at least 12 h of 5% dextrose in 0.45% NaCl at a rate of 1 ml/kg per h before the catheterization. All patients received 12 h of intravenous fluids after the procedure. Four (10.8%) of 37 patients in the bolus therapy arm developed CIN compared with none of the 26 patients who received sustained intravenous fluid ($P = 0.136$). These findings suggest that administration of intravenous fluids over a sustained period of time may be more protective than bolus fluid supplementation; however, the lack of comparability in the volume and composition of intravenous fluid administered to the two groups limits the study's conclusion on the independent effect of timing and duration of therapy. Moreover, the small sample size limits the power of this trial.

In a very similar study, Bader *et al.* (34) randomly assigned 39 patients who had normal renal function and were undergoing radiographic procedures with intravascular radiocontrast to receive either 2000 ml of intravenous saline over 12 h before and 12 h after the procedure or a bolus of 300 ml of intravenous saline at the time of radiocontrast administration. Mean GFR decreased to a greater degree in the bolus infusion group compared with the continuous infusion cohort (34.6 versus 18.3 ml/min per 1.73 m²; $P < 0.05$), whereas a slightly greater proportion of patients who received bolus fluids demonstrated a decrease in GFR of $>50\%$ (15 versus 5.3%; $P = 0.605$). None of the study patients required renal replacement therapy. Although this trial, like that of Krasuski *et al.* (33), suggested a possible benefit to sustained intravenous fluid supplementation, the small number of patients substantially limits the study's power.

The hypothesis that intravenous fluid that contains sodium bicarbonate might decrease the incidence of CIN compared with NaCl was recently tested in three randomized trials (11,35,36). The hypothesis for a potential benefit of bicarbonate is based on the concept that alkalinizing tubular fluid reduces the generation of injurious hydroxyl radicals. In the first of these trials, Merten *et al.* (11) randomly assigned patients to receive either isotonic NaHCO₃ or isotonic NaCl at a rate of 3 ml/kg per h for 1 h before and 1 ml/kg per h for 6 h after the administration of intravascular radiocontrast. Using an increase in SCr of $\geq 25\%$ within 48 h to define CIN, one of 60 patients

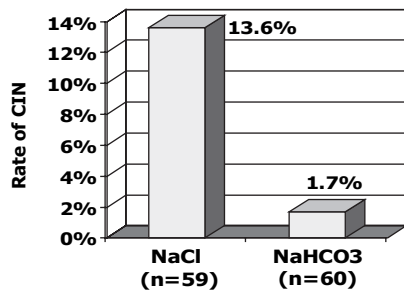


Figure 2. Incidence of contrast-induced nephropathy (11).

who received NaHCO₃ developed this complication, compared with eight of 59 patients who were randomly assigned to receive NaCl (1.7 versus 13.6%; $P = 0.02$; Figure 2). The study was stopped at an interim analysis; however, an additional 191 patients who received a comparable sodium bicarbonate protocol demonstrated a rate of CIN of 1.6%. It is important to note that the threshold designated for study termination was not explicitly stated, and the relatively small number of study participants increased the possibility that the primary result could have represented a false-positive finding. Nonetheless, the rate of CIN among postrandomization registry patients was nearly identical to that observed in patients who had been randomly assigned to receive NaHCO₃, supporting the validity of the findings. This study also demonstrated a very low rate of CIN associated with an abbreviated intravenous fluid regimen.

More recently, Briguori *et al.* (35) randomly assigned 326 patients who had CKD and were undergoing coronary or peripheral angiography to receive intravenous isotonic sodium bicarbonate with N-acetylcysteine (NAC) or intravenous isotonic sodium chloride with NAC alone or NAC and ascorbic acid. Sodium bicarbonate fluids were administered according to the protocol used by Merten *et al.*, whereas saline was administered at 1 ml/kg per h for 12 h before and 12 h after the procedure. CIN occurred in 1.9% of patients who received bicarbonate/NAC, 9.9% of patients who received saline/NAC, and 10.3% of patients who were administered saline/NAC/ascorbic acid ($P = 0.019$ for comparison of bicarbonate/NAC with saline/NAC). The findings of this study along with those of Merten *et al.* provide evidence supporting the use of bicarbonate-based fluids; however, both trials enrolled relatively small numbers of patients and lacked sufficient statistical power to establish conclusively bicarbonate infusion as a superior regimen. In fact, in both of these studies, the occurrence of one more episode of CIN in the bicarbonate groups and one fewer in the saline groups would have rendered the results nonstatistically significant. Adequately powered studies that address this question will be required to validate these early findings.

Last, a very recent study by Recio-Mayoral *et al.* (36) in 111 patients who were undergoing emergent coronary procedures compared intravenous isotonic sodium bicarbonate mixed with NAC with intravenous saline for the prevention of CIN. Both groups also received oral NAC after the procedure. CIN was observed in 1.8% of patients in the bicarbon-

ate group compared with 21.8% in the saline group ($P < 0.001$); however, there were important differences in the groups that may explain this finding. First, patients in the bicarbonate group received preprocedure volume expansion (5 ml/kg per h for 1 h), which was not administered to the saline group, as well as a higher rate of postprocedure fluids than the saline group (1.5 versus 1 ml/kg per h). Second, intravenous NAC was administered to the bicarbonate group but not to those who received saline; therefore, conclusions on the optimal fluid composition cannot be drawn from these results. Of note, one study in 96 pediatric patients found that urinary alkalization with acetazolamide (administered with isotonic NaCl) led to a lower incidence of CIN than intravenous isotonic sodium bicarbonate (0.0 versus 8.7%; $P = 0.049$) (37); however, this study was conducted in children, in whom CIN is less frequent, and enrolled a small number of patients. Future, well-powered studies in adults will be needed to elucidate better the role of urinary alkalization, whether by exogenous alkali or by carbonic anhydrase inhibition.

Clinical Trials of Oral Fluid/Solute

A large proportion of procedures that use intravascular radiocontrast are performed on an outpatient and elective basis. The financial barriers to routine hospital admission for intravenous volume expansion and the feasibility of prolonged intravenous fluid administration in outpatient radiology departments and cardiac angiography suites have led to efforts to assess the effectiveness of oral volume supplementation for the prevention of CIN (Table 2).

The Preparation for Angiography in Renal Dysfunction (PREPARED) study examined the efficacy of an outpatient fluid regimen in the setting of elective coronary angiography (38). Eighteen patients were randomly assigned to an outpatient regimen that consisted of 1000 ml of water orally over 10 h before catheterization along with 300 ml/h of 0.45% intravenous NaCl started 30 to 60 min before the procedure and continued for 6 h afterward. The 18 study patients who were randomly assigned to the inpatient regimen received 0.45% NaCl intravenously for 12 h before and 12 h after angiography. Maximal change in SCr up to 48 h after the procedure, which was the primary study outcome, was similar in the two study groups (0.12 mg/dl for outpatient therapy versus 0.21 mg/dl in the inpatient group; NS). The principal conclusion of this study was that an outpatient regimen (oral fluid followed by peri- and postprocedural intravenous fluid) is as effective as an inpatient course of intravenous fluid. Although the use of a continuous variable to define the primary end point improved the power to detect differences between the study groups and allowed for the recruitment of a small number of patients compared with the number that would likely have been required using a dichotomous end point, the observed difference in this study's primary end point between the study groups may not be clinically relevant. Moreover, it must be recognized that the absence of a statistical difference between groups in a small study is not the same as a demonstration of equivalence between treatments. Statistical principles dictate a need for large sample sizes to have adequate power to establish equiv-

Table 2. Randomized trials of oral fluid/solute supplementation

Study	No. of Patients	Oral Volume Regimen	Intravenous Fluid Regimen	Baseline SCr (mg/dl)	Rate of CIN (Oral versus Intravenous)	P
Taylor <i>et al.</i> (40)	36	1000 ml of H ₂ O for 10 h ^a	0.45% NaCl 75 ml/h for 24 h	1.74 to 1.75	6 versus 11%	NS
Trivedi <i>et al.</i> (13)	53	Unrestricted oral fluids	0.9% NaCl 1 ml/kg per h for 24 h	1.14 to 1.27	34.6 versus 3.7%	0.005
Dussol <i>et al.</i> (39)	353	1 g/10 kg per d NaCl for 2 d	0.9% NaCl 15 ml/kg for 6 h	2.15 to 2.42	6.6 versus 5.2%	NS

^aIncluded 300 ml of intravenous 0.45% NaCl begun 30 to 60 min before radiocontrast administration and continued for 6 h.

absence. Thus, the absence of a difference in a small study, as observed between the oral-based fluid regimen and an inpatient intravenous fluid regimen in the PREPARED study, does not establish the equivalence of these two interventions.

In a subsequent trial, Trivedi *et al.* (13) compared the effects of intravenous and oral fluid in a cohort of patients who were undergoing nonemergent coronary angiography. Patients were randomly assigned to receive either intravenous 0.9% NaCl for 12 h before and 12 h after angiography or unrestricted oral fluids. Although the study protocol was designed to randomly assign a total of 160 patients, the study was stopped at an interim analysis after 53 patients had been enrolled, when the rate of CIN was found to be substantially greater in the unrestricted oral fluid group compared with the intravenous fluid group (34.6 versus 3.7%; $P = 0.005$). Although the change in patients' weight was similar in the two study arms, the volume of fluid consumed by those who were randomly assigned to the oral fluid study arm was not reported. Moreover, the baseline creatinine clearance in the two study arms, 76.2 and 83.1 ml/min, suggested relatively intact kidney function among study participants. Given the relatively low risk for AKI in this study population, the development of CIN in 34.6% of patients who were randomly assigned to unrestricted oral fluids is surprising.

More recently, Dussol *et al.* (39) conducted a multiarm trial to compare the rate of CIN among 312 patients with stage 3 or 4 CKD. Patients were randomly assigned to receive one of four preventive regimens before radiocontrast administration: 2 d of oral NaCl (1 g/10 kg per d), 6 h of intravenous 0.9% NaCl (15 ml/kg), or this same intravenous NaCl regimen with either 5 mg/kg of oral theophylline 1 h before the procedure or intravenous furosemide (3 mg/kg) just after the procedure. The rate of CIN was 6.6% in the oral NaCl group, 5.2% in the intravenous fluid group, 7.5% in the theophylline group, and 15.2% in the furosemide arm. The difference in CIN between the oral NaCl and intravenous NaCl groups was not found to be statistically significant, yet intravenous NaCl alone was associated with a lower rate of CIN than intravenous NaCl with furosemide, a finding similar to that of the study by Solomon *et al.* (10). Of note, no study patients were reported to have developed overt volume overload, significant hypertension, or the need for renal replacement therapy. Using a hypothetical 70-kg patient who was randomly assigned to the oral NaCl group, 240 mEq of NaCl would have been ingested over 2 d, a dosage of NaCl equivalent to approximately 1.5 L of isotonic saline. Assuming that patients were compliant with oral NaCl intake, this study achieved a robust degree of extracellular volume expansion in the oral intervention group, which contrasts somewhat with the PREPARED study, in which the intake of water likely led primarily to intracellular volume expansion.

In summary, there are insufficient data to support the substitution of oral water for intravenous fluids in high-risk patients. The study by Dussol *et al.* (39) provides early evidence that a preprocedure volume expansion regimen composed primarily of oral NaCl, which would be feasible to administer to an outpatient, may provide comparable protection to an inpatient intravenous fluid regimen. There is an overall lack of

statistical power in these studies to determine conclusively that orally administered volume supplementation is equivalent to intravenous fluid regimens. Future studies will need to explore in greater detail the precise role and benefit of oral fluid prophylaxis for CIN.

Conclusions

Cumulative data from animal studies, observational analyses, and randomized clinical trials have helped to establish the beneficial effect of volume expansion on reducing the risk for CIN. Although the precise mechanisms by which volume supplementation exerts a protective effect remain unknown, isotonic intravenous fluid offers greater benefit than hypotonic fluid. The use of isotonic NaHCO₃ has been found in a few recent studies to provide a potential advantage over equimolar NaCl, and its infusion over a relatively short period of time before and after the radiocontrast procedure seems effective. Additional confirmatory studies are necessary before there will be sufficient evidence to establish an abbreviated bicarbonate-based intravenous fluid regimen as the standard of care. At the present time, our recommendations include the administration of either isotonic sodium chloride or sodium bicarbonate at a rate of 1 ml/kg per h for 12 h before and 12 h after radiocontrast administration in high-risk hospitalized patients and eligible outpatients who are undergoing nonemergent procedures, independent of type of radiocontrast or route of administration. An abbreviated regimen of isotonic fluid (3 ml/kg per h for 1 h before the procedure and 1 ml/kg per h for 6 h after the procedure) can be administered to patients who undergo more urgent procedures or for whom sustained volume expansion is not possible. For patients who undergo emergent procedures in which the administration of intravascular radiocontrast is required and preprocedure volume expansion is not possible, a sustained period of isotonic fluid administration after the procedure is advisable. The role of oral volume supplementation to prevent CIN continues to evolve, yet its potential efficacy seems promising if supplemented with oral sodium chloride. At the present time, the evidence base is not sufficiently robust to recommend enteral fluid prophylaxis alone; however, patients who are at increased risk for CIN should be encouraged to liberalize their oral fluid and solute intake to augment the volume-expansive effects of intravenous fluids. There remains a clear need for well-powered studies with large numbers of high-risk patients to help answer the outstanding questions of composition, route of administration, rate, and duration of volume expansion to prevent CIN.

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