

Sodium Bicarbonate Versus Sodium Chloride for Preventing Contrast-Associated Acute Kidney Injury in Critically Ill Patients: A Randomized Controlled Trial

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Objectives: To test whether hydration with bicarbonate rather than isotonic sodium chloride reduces the risk of contrast-associated acute kidney injury in critically ill patients.

Design: Prospective, double-blind, multicenter, randomized controlled study.

Setting: Three French ICUs.

Patients: Critically ill patients with stable renal function ($n = 307$) who received intravascular contrast media.

Interventions: Hydration with 0.9% sodium chloride or 1.4% sodium bicarbonate administered with the same infusion protocol: 3 mL/kg during 1 hour before and 1 mL/kg/hr during 6 hours after contrast medium exposure.

Measurements and Main Results: The primary endpoint was the development of contrast-associated acute kidney injury, as defined by the Acute Kidney Injury Network criteria, 72 hours after

contrast exposure. Patients randomized to the bicarbonate group ($n = 151$) showed a higher urinary pH at the end of the infusion than patients randomized to the saline group ($n = 156$) (6.7 ± 2.1 vs 6.2 ± 1.8 , respectively; $p < 0.0001$). The frequency of contrast-associated acute kidney injury was similar in both groups: 52 patients (33.3%) in the saline group and 53 patients (35.1%) in the bicarbonate group (absolute risk difference, -1.8% ; 95% CI $[-12.3\% \text{ to } 8.9\%]$; $p = 0.81$). The need for renal replacement therapy (five [3.2%] and six [3.9%] patients; $p = 0.77$), ICU length of stay (24.7 ± 22.9 and 23 ± 23.8 d; $p = 0.52$), and mortality (25 [16.0%] and 24 [15.9%] patients; $p > 0.99$) were also similar between the saline and bicarbonate groups, respectively.

Conclusions: Except for urinary pH, none of the outcomes differed between the two groups. Among ICU patients with stable renal function, the benefit of using sodium bicarbonate rather than isotonic sodium chloride for preventing contrast-associated acute kidney injury is marginal, if any. (*Crit Care Med* 2017; 45:637–644)

Key Words: acute kidney injury; contrast media; critical care; sodium bicarbonate; sodium chloride

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Critically ill patients are exposed to multiple and often unavoidable kidney injury such as sepsis, shock, and nephrotoxic medications. Acute kidney injury (AKI) is therefore a common complication in ICUs. Up to half of critically ill patients are either admitted with AKI or subsequently developed this complication during their ICU stay (1, 2). AKI is reported to be an independent risk factor for mortality, which increases with the severity of AKI especially when renal replacement therapy is needed (3, 4).

Contrast-associated AKI (CA-AKI) is reported to be the third leading cause of AKI in hospitalized patients (5). The morbidity and mortality associated with CA-AKI are well-known phenomena outside of the ICU. Indeed, there is a higher need for

renal replacement therapy, longer hospital length of stay, and higher in-hospital mortality for patients who develop CA-AKI compared with those who do not (6, 7). Current guidelines consider IV volume expansion to be the cornerstone treatment for the prevention of CA-AKI (8, 9). Isotonic sodium chloride and sodium bicarbonate have been studied for this indication in non-ICU patients with conflicting results regarding the superiority of bicarbonate over saline (10–13).

Few trials have explored strategies for the prevention of CA-AKI in the ICU, and no study has compared sodium chloride with sodium bicarbonate for the optimization of volume status. The international consensus conference on the prevention and management of acute renal failure in ICU patients recommends using isotonic sodium chloride or preferably sodium bicarbonate for CA-AKI prevention in high-risk patients, while emphasizing that the safety and efficacy of bicarbonate need to be assessed in further studies (8). Thus, the objective of the HYDRAREA study was to test whether sodium bicarbonate is superior to isotonic sodium chloride for preventing CA-AKI in critically ill patients.

MATERIALS AND METHODS

Design and Population

The HYDRAREA study was a prospective, multicenter, double-blind, randomized controlled trial conducted in France from February 2012 through January 2015. Two ICUs were medical and surgical ICU in a teaching hospital, and one ICU was a medical and surgical ICU in a general hospital. The study protocol was approved by the local Ethics Committee (Comité de Protection des Personnes nord ouest III, no. 2011-A00227-34). Written informed consent was obtained from patients or their relatives in cases of impaired decision-making capacity at the time of enrollment.

Eligible patients were consecutive adults (≥ 18 yr) who underwent imaging with intravascular contrast medium and had an expected ICU length of stay of more than 48 hours. Patients could be included only once. To limit bias related to confounding factors, patients with unstable renal function defined as a serum creatinine increase greater than or equal to 0.3 mg/dL within the previous 48 hours or anuria within the previous 12 hours were not included. To secure renal function stability during at least 1 day, patients were not included on the day of ICU admission. Other exclusion criteria were as follows: patients under renal replacement therapy at the time of enrollment; patients with safety concerns about volume expansion or bicarbonate load, such as uncontrolled cardiogenic pulmonary edema, chronic hypercapnia, metabolic alkalosis with pH greater than 7.50 or hypokalemia less than 3 mmol/L; pregnancy; patients with an expected lifetime less than 5 days; patients with treatment-limitation decision; patients under guardianship; and patients who were unable to provide consent.

Randomization and Study Protocol

Eligible patients were randomly assigned in a 1:1 ratio to receive either 0.9% sodium chloride (Chlorure de sodium Lavoisier, 0.9%, Paris, France) or 1.4% sodium bicarbonate

(Bicarbonate de sodium Lavoisier, 1.4%, Paris, France) via the use of permuted blocks of size four. The randomization was stratified on the ICU. Glass bottles containing 500 mL of sodium chloride or sodium bicarbonate were anonymized by the pharmacist and had the same appearance in support of the double-blinded design. The infusion protocol was identical for both solutions: 3 mL/kg during 1 hour started before the administration of contrast medium followed by 1 mL/kg/hr for 6 hours after contrast exposure (10). No other CA-AKI prevention therapies were permitted during the study period.

Data Collection

Details on data collection are provided in the **Supplementary Appendix** (Supplemental Digital Content 1, <http://links.lww.com/CCM/C398>).

Study Endpoints

The primary endpoint was the development of CA-AKI as defined by an increase in serum creatinine equal or more than 0.3 mg/dL or 50% compared with the serum creatinine at inclusion or a urinary output of less than 0.5 mL/kg/hr for 6 hours within 72 hours after contrast exposure. This definition corresponds to the AKI Network (AKIN) criteria (14) with a different timeframe of 72 hours that is usually applied to define CA-AKI.

We conducted several sensitivity analyses regarding the primary endpoint. First we conducted a multivariate analysis of the primary endpoint according to the AKIN criteria, controlling for potential confounders. Second, we computed multiple imputations of the primary endpoint according to the AKIN criteria in the intent-to-treat dataset. Third, we compared the primary endpoint between groups using alternative definitions of CA-AKI (details provided in the **Supplementary Appendix**, Supplemental Digital Content 2, <http://links.lww.com/CCM/C398>).

The secondary endpoints were urinary pH at the end of hydration, the need for renal replacement therapy, ICU length of stay, and ICU mortality. The initiation of renal replacement therapy, either hemodialysis or continuous venovenous hemofiltration, was left to the discretion of the attending physician.

Statistical Analysis

Regarding the primary endpoint, that is, CA-AKI, we assumed an incidence of 15% in the saline group, based on a pilot study performed in one of the participating ICUs (15), and an incidence of 5% in the bicarbonate group, based on previous studies conducted outside the ICU (10, 16–19), corresponding to a 10% absolute difference in risk. Considering a two-tailed α of 0.05 and a β of 0.20, we calculated that overall 282 patients were required; therefore, we planned to include 300 patients.

The main analysis included all randomized patients who followed the inclusion criteria, that is, a modified intention-to-treat strategy. Baseline characteristics were described by numbers (%), means (95% CI), or medians (interquartile range), as appropriate. The primary outcome was compared between groups with a Fisher exact chi-square test. Details on the statistical analysis are provided in the **Supplementary Appendix** (Supplemental Digital Content 3, <http://links.lww.com/CCM/>

C398). We used SAS software 9.4 (SAS Institute, Cary, NC) and a *p* value of less than 0.05 to denote statistical significance.

RESULTS

Of the 1,458 patients assessed for eligibility, 320 were randomized (Fig. 1). Among those, 13 patients (4.1%) were subsequently excluded because they did not meet the inclusion criteria. Consequently, 307 patients (95.9%) were included in the modified intention-to-treat analysis with 156 patients in the sodium chloride group and 151 patients in the sodium bicarbonate group; 320 patients (100%) were included in the intention-to-treat sensitivity analysis with multiple imputations.

Baseline and Procedural Characteristics

Patients in the sodium chloride and sodium bicarbonate groups had similar baseline characteristics (Table 1). Patient characteristics at randomization were well balanced between the groups except for the use of nephrotoxic medications which was more common in the sodium chloride group (Table 1). This imbalance was related to a higher administration of vancomycin and aminoglycosides in the saline group (eTable 1, Supplemental

Digital Content 4, <http://links.lww.com/CCM/C398>). Procedural and patient characteristics in the 72 hours following contrast exposure were similar, including the overall use of nephrotoxic medications (Table 1) (eTable 2, Supplemental Digital Content 5, <http://links.lww.com/CCM/C398>). Low-osmolar contrast medium was used in 276 patients, whereas other patients received iso-osmolar or unknown contrast.

Serum bicarbonate, serum pH, and urinary pH were similar between the groups before hydration (Fig. 2) (eFig. 1, Supplemental Digital Content 6, <http://links.lww.com/CCM/C398>; and eFig. 2, Supplemental Digital Content 7, <http://links.lww.com/CCM/C398>). The median amount of fluid given for prevention was 693 mL (576–783) and 702 mL (594–783) for the bicarbonate and saline groups, respectively. The urinary pH at the end of the hydration procedure was significantly higher in the bicarbonate group than in the saline group (6.7 ± 2.1 vs 6.2 ± 1.8 , respectively; $p < 0.0001$) (Fig. 2).

Primary Endpoint

The overall evolution of serum creatinine and urine output during follow-up was similar between groups (eFig. 3, Supplemental Digital Content 8, <http://links.lww.com/CCM/C398> and eFig. 4, Supplemental Digital Content 9, <http://links.lww.com/CCM/C398>). CA-AKI as defined by the AKIN criteria occurred in 52 patients (33.3%) in the sodium chloride group and in 53 patients (35.1%) in the sodium bicarbonate group (absolute difference, -1.8% ; 95% CI $[-12.3\% \text{ to } 8.9\%]$; $p = 0.81$) (Table 2). In the multivariate sensitivity analysis, the hydration protocol was not associated with the occurrence of CA-AKI (adjusted odds ratio [aOR], 0.94; 95% CI $[0.57\text{--}1.58]$; $p = 0.81$), controlling for age (aOR for 10-yr increase, 1.22; 95% CI $[1.02\text{--}1.45]$; $p = 0.03$), Sequential Organ Failure Assessment score at inclusion (aOR for 1 additional organ failure, 1.14; 95% CI $[1.06\text{--}1.23]$; $p < 0.001$), no sepsis at inclusion (aOR vs sepsis, 1.9; 95% CI $[1.0\text{--}3.5]$; $p = 0.043$), Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage renal disease classification at inclusion (aOR for 1 grade increase, 1.9; 95%

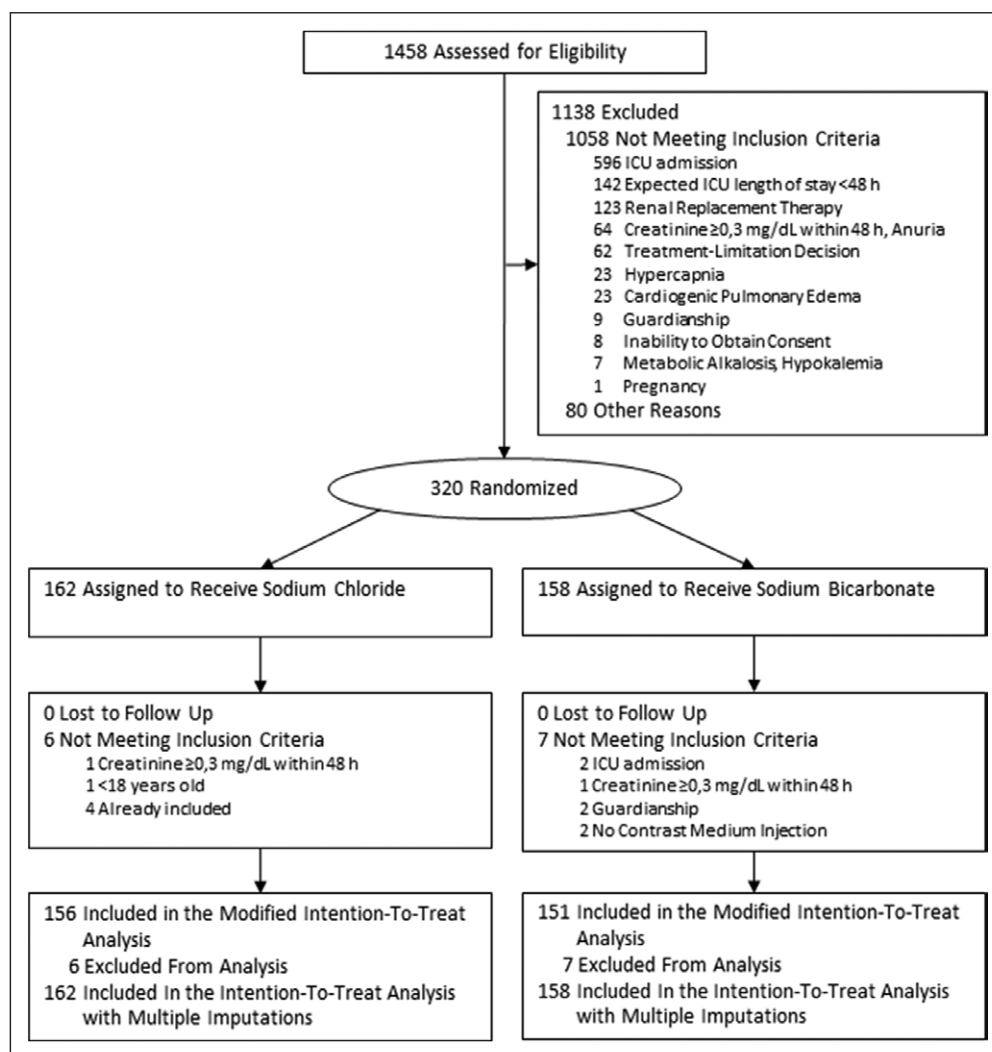


Figure 1. Flow diagram of the HYDRAREA study.

TABLE 1. Patient Characteristics

Characteristics	Sodium Chloride (n = 156)	Sodium Bicarbonate (n = 151)
Baseline		
Age, mean (SD) years	56.6 (14.3)	55.8 (15.5)
Male sex, n (%)	103 (66.0)	105 (69.5)
Body mass index, median (IQR) kg/m ²	24.9 (22–29.4)	26.3 (22.8–29.9)
Baseline serum creatinine ^a , median (IQR) mg/dL	1 (0.81–1.1)	0.98 (0.81–1.1)
Chronic kidney disease ^b , n (%)	2 (1.2)	5 (3.3)
Diabetes mellitus, n (%)	20 (12.8)	21 (13.9)
Hypertension, n (%)	69 (44.2)	56 (37.0)
Congestive heart failure ^c , n (%)	10 (6.4)	10 (6.6)
At ICU admission		
Simplified Acute Physiology Score II, median (IQR)	40.5 (28–50.5)	41.0 (31–54)
SOFA, median (IQR)	7 (4–10)	7 (4–9)
Admission diagnosis		
Medical, n (%)	68 (43.5)	64 (42.3)
Scheduled surgery, n (%)	3 (1.9)	9 (5.9)
Emergency surgery, n (%)	61 (39.1)	57 (37.7)
Trauma, n (%)	24 (15.3)	21 (13.9)
At randomization		
Time from ICU admission to randomization, median (IQR) day	4 (1–9)	3 (1–8)
SOFA, median (IQR)	4 (2–7)	4 (2–7)
Mechanical ventilation, n (%)	123 (78.8)	120 (79.4)
Catecholamine, n (%)	52 (33.3)	48 (31.7)
Sepsis ^d , n (%)	59 (37.8)	45 (29.8)
Serum creatinine, median (IQR) mg/dL	0.7 (0.55–0.95)	0.69 (0.56–0.84)
Daily urine output, median (IQR) mL/24 hr	1700 (1200–2500)	1670 (1100–2500)
Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage renal disease classification ≥ risk of kidney injury class, n (%)	19 (12.1)	21 (13.9)
Nephrotoxic medication ^e , n (%)	59 (37.8)	40 (26.4)
Contrast injection in the prior 72 hr, n (%)	45 (28.8)	52 (34.4)
Procedure		
CT, n (%)	97 (62.1)	96 (63.5)
Arteriography, n (%)	59 (37.8)	55 (36.4)
Low-osmolar contrast medium ^f , n (%)	142 (91.0)	134 (88.7)
Contrast medium volume, median (IQR) mL	90 (70–110)	90 (70–100)

IQR = interquartile range, SOFA = Sequential Organ Failure Assessment.

^aEstimated assuming a glomerular filtration rate of 75 mL/min per 1.73 m² using the modification of diet in renal disease (MDRD) equation in 219 patients because of unknown baseline serum creatinine.

^bDefined by glomerular filtration rate < 60 mL/min per 1.73 m² using the MDRD equation.

^cDefined by left ventricular ejection fraction < 50% or New York Heart Association class III or IV heart failure.

^dKnown or presumed infection with two or more criteria of the systemic inflammatory response syndrome.

^ep < 0.05 between groups.

^flomeprol, ioxaglate, iohexol, iobitridol, ioversol, iopromide.

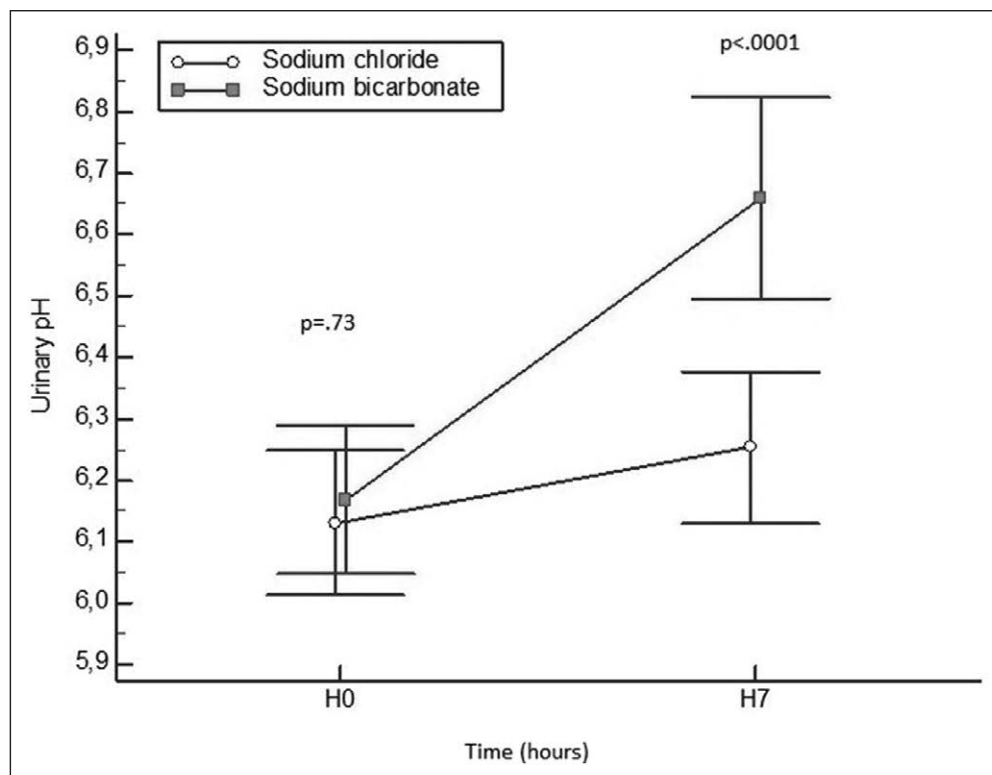


Figure 2. Mean urinary pH according to the hydration strategy. Comparisons at H0 and H7 of urinary pH according to the hydration strategy. Results are presented as means (sd).

CI [0.9–3.8]; $p = 0.09$), arteriography (aOR vs CT, 0.8; 95% CI [0.4–1.4]; $p = 0.38$), diabetes (aOR, 1.4; 95% CI [0.7–3.0]; $p = 0.33$), and nephrotoxic medications (aOR, 1.3; 95% CI [0.7–2.5]; $p = 0.33$).

The result of the sensitivity analysis in the intent-to-treat dataset using multiple imputations ($n = 320$) was similar to the results of the main analysis (OR, 1.04; 95% CI [0.82–1.32];

DISCUSSION

In this randomized clinical trial, preventive hydration with sodium bicarbonate did not alter the frequency of CA-AKI in critically ill patients compared with isotonic sodium chloride, despite its effect on urine alkalization. Furthermore, no benefits were found in terms of the requirement for renal replacement therapy, ICU length of stay, and mortality.

$p = 0.75$). The use of an alternative definition of CA-AKI (Table 2) also led to consistent results.

Secondary Endpoints

The need for renal replacement therapy (five [3.2%] vs six [3.9%] patients; $p = 0.77$), ICU length of stay (24.7 ± 22.9 vs 23 ± 23.8 d; $p = 0.52$), and ICU mortality (25 [16.0%] vs 24 [15.9%] patients; $p > 0.99$) was similar between the saline and bicarbonate groups, respectively (Table 2). No difference was found in the safety profile resulting from each regimen as assessed by the incidence of cardiac arrest, cardiogenic pulmonary edema, and hypokalemia (eTable 2, Supplemental Digital Content 5, <http://links.lww.com/CCM/C398>).

TABLE 2. Primary Endpoint With Sensitivity Analyses and Secondary Endpoints

	Sodium Chloride ($n = 156$) (%)	Sodium Bicarbonate ($n = 151$) (%)	Absolute Risk Difference (95% CI)	p
Primary endpoint	52 (33.3)	53 (35.1)	-1.8% (-12.3 to 8.9)	0.81
Sensitivity analysis of the primary endpoint using alternative definitions of contrast-associated AKI				
AKI Network criteria within 72 hr without urine output criteria, n (%)	10 (6.4)	16 (10.6)	-4.2% (-10.8 to 2.2)	0.22
Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage renal disease classification definition, n (%)	48 (30.8)	48 (31.8)	-1.0% (-11.3 to 9.3)	0.90
Increase in serum creatinine > 0.5 mg/dL or 25%, n (%)	19 (12.2)	28 (18.5)	-6.4% (-14.5 to 1.8)	0.15
Secondary endpoints				
Renal replacement therapy, n (%)	5 (3.2)	6 (3.9)	-0.8% (-5.6 to 3.8)	0.77
Length of ICU stay, mean (sd), d	24.7 (22.9)	23.0 (23.8)	1.7 (-3.5 to 7.0)	0.53
ICU mortality, n (%)	25 (16.0)	24 (15.9)	0.1% (-8.2 to 8.4)	> 0.99

AKI = acute kidney injury.

The pathophysiology of CA-AKI is complex and involves several pathways that lead to kidney injury (20, 21). One of the main routes is related to the hyperosmolar feature of contrast medium, which promotes a tubuloglomerular feedback inducing renal vasoconstriction and ultimately a reduction in renal blood flow. Furthermore, the phenomenon of ischemic-reperfusion generates oxygen free radicals that worsen the renal insult. It is unknown to what extent these reactive oxygen species are involved in the development of CA-AKI compared with other processes. The cornerstone of CA-AKI prevention is isotonic volume expansion, which attenuates the tubuloglomerular feedback and the decrease in renal blood flow. Alkalinization with bicarbonate perfusion may in theory attenuate the production of hydroxyl radicals by limiting the Haber-Weiss and Fenton reactions, which are most active at an acid pH, and thus reduce reactive oxygen species formation (21). In a randomized clinical trial, Merten et al (10) compared isotonic sodium chloride and sodium bicarbonate for CA-AKI prevention. Their study was stopped early because of a significant reduction in the occurrence of CA-AKI from 13.6% to 1.7%. However, subsequent studies reported conflicting results (11, 16–19, 22–34). In meta-analyses, a lower incidence of CA-AKI was found in patients receiving bicarbonate compared with saline (12, 13, 35–38). It should be noted that the heterogeneity between studies was substantial, especially regarding periprocedural hydration protocols, concurrent medications, contrast medium used, and radiographic procedures. Furthermore, the beneficial effect of bicarbonate was higher in the smaller and published studies, suggesting publication bias. Therefore, uncertainty persists about the superiority of bicarbonate over saline, and Kidney Disease Improving Global Outcome guidelines recommend IV volume expansion with isotonic sodium chloride or sodium bicarbonate for CA-AKI prevention (9). It should be emphasized that the majority of these studies used contrast during cardiac catheterization in populations that differed from critically ill patients. The HYDRAREA study was the first to investigate the safety and efficacy of bicarbonate for CA-AKI prevention in the ICU. Despite a hydration protocol similar to the study by Merten et al (10), bicarbonate infusion did not provide greater protection against CA-AKI than saline in our critically ill population. Our bicarbonate solution had a different concentration than that used in previous studies (168 vs 154 mEq/L, respectively) in which the bicarbonate solution was prepared by mixing hypertonic bicarbonate with a dextrose solution (11, 16, 18, 19, 26–30). These self-made preparations are time consuming and carry a risk of dosing error (9). Consequently, we chose to use a commercial 1.4% sodium bicarbonate solution that does not have the same risk in spite of a higher bicarbonate and sodium concentration. Furthermore, our chosen solution resulted in a satisfying urine alkalinization with a mean urinary pH of 6.7 at the end of the infusion.

Deterioration of kidney function after injection of intravascular contrast medium is frequent in critically ill patients, and the occurrence rate of CA-AKI in this setting greatly depends of the definition used (15, 39–42). In our study, the frequency of CA-AKI found of 34% was in accordance with the results of

recent studies conducted in the ICU using the same CA-AKI definition and case mix (41, 42). To explore the impact of alternative CA-AKI definitions, we performed several sensitivity analyses using several definitions of CA-AKI with or without urinary output criteria with consistent results. Furthermore, it is necessary to evaluate for other possible etiologies of AKI following an increase in serum creatinine after the administration of contrast in critically ill patients who often have many factors that can influence kidney function (9). These factors were frequent in our population, and no differences between the groups were found except for the greater use of vancomycin and aminoglycosides at randomization in the saline group. Therefore, it is unlikely that the absence of superiority of bicarbonate in comparison to saline was related to confounding factors. Furthermore, the stability of kidney function in the previous 48 hours was required before patient inclusions limiting confusion bias related to progressive alteration of kidney function before the administration of contrast medium.

The present study has some limitations that should be emphasized. First, we assumed an incidence of CA-AKI of 15% in the saline group, which was lower than the observed rate of 33% that made our study underpowered. Few data on the epidemiology of CA-AKI in the ICU were available when we planned the study, and we assumed an occurrence rate of CA-AKI based on a preliminary study performed in the ICU but with a different case mix (15). No differences between the groups were seen in our study, and the higher occurrence rate of CA-AKI was numerically observed in patients receiving bicarbonate. Accordingly, a statistically significant positive effect of bicarbonate for preventing CA-AKI in ICU is unlikely even with a larger population. Thus, the HYDRAREA study provides new information for clinical practice despite an inadequate power to demonstrate small differences. Second, physicians were not blinded to the measurements of urinary pH, which could have jeopardized the double-blind design. Documentation of urinary pH was essential for the interpretation of our results, especially because the findings were negative. Furthermore, our primary outcome based on measurements of serum creatinine and urine output was objective. Third, despite a multicenter design, only three ICUs in the same country participated to the HYDRAREA study, which could compromise the generalization of our results. However, patients were recruited in academic and nonacademic general hospitals, and the case mix was well balanced between medical, surgical, and trauma patients. Fourth, we cannot exclude a beneficial effect of sodium bicarbonate in specific subpopulations of ICU patients, such as those with several risk factors for CA-AKI or those with unstable renal function. To increase the homogeneity of the groups being compared, our study only selected patients with stable renal function. Finally, because of the well-known multifactorial origin of AKI in critically ill patients, it is difficult to know precisely in what extent contrast medium led to AKI in our studied population (43, 44). It could be possible that the bicarbonate hydration did not improve the outcome because the outcome was not related to the insult the infusion therapy was trying to prevent.

CONCLUSIONS

In conclusion, among critically ill patients who received intravascular contrast medium, sodium bicarbonate hydration did not provide additional benefits compared with isotonic sodium chloride for CA-AKI prevention, subsequent need for renal replacement therapy, ICU length of stay, and ICU mortality.

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