Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults

Nor'azim Mohd Yunos, MD

Rinaldo Bellomo, MD, FCICM

Colin Hegarty, BSc

David Story, MD

Lisa Ho, MClinPharm

Michael Bailey, PhD

THE ADMINISTRATION OF INTRAvenous chloride is ubiquitous in critical care medicine.[1,2] In addition, many of the fluids used for hydration and resuscitation contain supraphysiological concentrations of chloride,[3-5] which induce or exacerbate hyperchloremia and metabolic acidosis,[6,7] may cause renal vasoconstriction and decreased glomerular filtration rate (GFR),[8-10] prolong time to first micturition,[11] and decrease urine output in major surgery.[12] Recently, in a double-blind randomized controlled trial, 2 L of saline decreased cortical perfusion in human study participants compared with Plasma-Lyte.[13] These effects of chloride on the kidney are of potential concern because acute kidney injury (AKI) is associated with high mortality[14] and may require treatment with costly and invasive renal replacement therapy (RRT).[15,16]

Given the high risk of AKI in critically ill patients and the experimental association between chloride administration and decreased renal function, we hypothesized that a chloride-restrictive intravenous fluids strategy in critically ill patients might be associated with

For editorial comment see p 1583.

Context Administration of traditional chloride-liberal intravenous fluids may precipitate acute kidney injury (AKI).

Objective To assess the association of a chloride-restrictive (vs chloride-liberal) intravenous fluid strategy with AKI in critically ill patients.

Design, Setting, and Patients Prospective, open-label, sequential period pilot study of 760 patients admitted consecutively to the intensive care unit (ICU) during the control period (February 18 to August 17, 2008) compared with 773 patients admitted consecutively during the intervention period (February 18 to August 17, 2009) at a university-affiliated hospital in Melbourne, Australia.

Interventions During the control period, patients received standard intravenous fluids. After a 6-month phase-out period (August 18, 2008, to February 17, 2009), any use of chloride-rich intravenous fluids (0.9% saline, 4% succinylated gelatin solution, or 4% albumin solution) was restricted to attending specialist approval only during the intervention period; patients instead received a lactated solution (Hartmann solution), a balanced solution (Plasma-Lyte 148), and chloride-poor 20% albumin.

Main Outcome Measures The primary outcomes included increase from baseline to peak creatinine level in the ICU and incidence of AKI according to the risk, injury, failure, loss, end-stage (RIFLE) classification. Secondary post hoc analysis outcomes included the need for renal replacement therapy (RRT), length of stay in ICU and hospital, and survival.

Results Chloride administration decreased by 144 504 mmol (from 694 to 496 mmol/patient) from the control period to the intervention period. Comparing the control period with the intervention period, the mean serum creatinine level increase while in the ICU was 22.6 μmol/L (95% CI, 17.5-27.7 μmol/L) vs 14.8 μmol/L (95% CI, 9.8-19.9 μmol/L) ($P = .03$), the incidence of injury and failure class of RIFLE-defined AKI was 14% (95% CI, 11%-16%; n=105) vs 8.4% (95% CI, 6.4%-10%; n=65) ($P < .001$), and the use of RRT was 10% (95% CI, 8.1%-12%; n=78) vs 6.3% (95% CI, 4.6%-8.1%; n=49) ($P = .005$). After adjustment for covariates, this association remained for incidence of injury and failure class of RIFLE-defined AKI (odds ratio, 0.52 [95% CI, 0.37-0.75]; $P < .001$) and use of RRT (odds ratio, 0.52 [95% CI, 0.33-0.81]; $P = .004$). There were no differences in hospital mortality, hospital or ICU length of stay, or need for RRT after hospital discharge.

Conclusion The implementation of a chloride-restrictive strategy in a tertiary ICU was associated with a significant decrease in the incidence of AKI and use of RRT.

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Author Affiliations: Johor Bahru Clinical School, Monash University Sunway Campus, Malaysia (Dr Yunos); Departments of Intensive Care (Dr Bellomo), Laboratory Medicine (Mr Hegarty), Anaesthesia (Dr Story), and Pharmacy (Ms Ho), Austin Hospital, Melbourne, Australia; and Australia and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia (Drs Bellomo and Bailey).
Corresponding Author: Rinaldo Bellomo, MD, FCICM, Austin Health, Heidelberg, Victoria 3084, Australia (rinaldo.bellomo@austin.org.au).

a decreased incidence and severity of AKI compared with a chloride-liberal intravenous strategy.

METHODS

We performed a prospective, open-label, before-and-after pilot study in the 22-bed multidisciplinary intensive care unit (ICU) of the Austin Hospital, a tertiary care hospital affiliated with the University of Melbourne. The study was conducted from February 18 to August 17, 2008 (control period), followed by a phase-out period (August 18, 2008, to February 17, 2009), and an intervention period (February 18 to August 17, 2009). No informed consent was obtained from patients because treatment was considered unit protocol–based and data collection required no direct patient contact. The study was approved by the human research ethics committee of the Austin Hospital with a waiver for informed consent because this was a practice change that applied to all admissions. The detailed methods have been described previously.[6]

Briefly, patients were admitted consecutively over 6 months during the control period and were given intravenous fluids according to clinician preferences with free use of chloride-rich fluids. These included 0.9% saline (chloride concentration: 150 mmol/L) (Baxter Pty Ltd), 4% succinylated gelatin solution (chloride concentration: 120 mmol/L) (Gelofusine, BBraun), and 4% albumin in sodium chloride (chloride concentration: 128 mmol/L) (4% Albumex, CSL Bioplasma).

Following a 6-month phase-out period that included education and preparation of all ICU staff and logistic arrangements for fluid accountability and delivery, the intervention period commenced with enrollment of all consecutive admissions in the next 6 months. No additional training was provided to nursing or medical staff. The intervention period replicated the same season of the year as the control period. Chloride-rich fluids (0.9% saline, 4% succinylated gelatin solution, or 4% albumin solution) were now made available

only after prescription by the attending specialist for specific conditions (eg, hyponatremia, traumatic brain injury, and cerebral edema).

In place of chloride-rich fluids, the following fluids were used: a lactated crystalloid solution (chloride concentration: 109 mmol/L) (Hartmann solution, Baxter Pty Ltd), a balanced buffered solution (chloride concentration: 98 mmol/L) (Plasma-Lyte 148, Baxter Pty), and a 20% albumin solution (chloride concentration: 19 mmol/L) (20% Albumex, CSL Bioplasma). Similar fluid changes were instituted in the emergency department but not in the operating rooms or general wards.

We collected age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II and III scores, Simplified Acute Physiology Score II (SAPS II), and multiple clinical characteristics of each admission for the patients enrolled. We retrieved pre-ICU admission serum creatinine levels and daily morning creatinine levels during ICU admission from the computerized central laboratory database. We also collected data on RRT, excluding patients with preexisting end-stage kidney disease who were receiving long-term dialysis and those treated with RRT for drug toxicity not associated with AKI. In RRT-treated survivors of ICU stay, we obtained data on dialysis status at 3 months after ICU discharge. Renal replacement therapy was initiated in the study unit according to the criteria of the Randomised Evaluation of Normal vs Augmented Level (RENAL) Replacement Therapy in ICU Trial.[17,18]

Primary outcomes included increase in creatinine from baseline to peak ICU level and incidence of AKI according to the risk, injury, failure, loss, end-stage (RIFLE) system definitions.[16,19] Secondary post hoc analysis outcomes included the need for RRT, length of stay in ICU and hospital, and survival.

We analyzed the increase in creatinine from baseline to peak levels in all patients. We used the creatinine levels to classify patients according to the RIFLE criteria.[16] The baseline creati-

nine level was based on the lowest creatinine level available in the 1-month period prior to ICU admission; when this was not available, creatinine level was estimated using the Modification of Diet in Renal Disease (MDRD) equation (assuming a lower limit of normal baseline GFR of 75 mL/min).[20]

Statistical Analysis

All statistical analysis was performed using Stata version 11 (StataCorp) and SAS version 9.2 (SAS Institute). Baseline comparisons were performed using χ^2 tests for equal proportion with results reported as numbers, percentages, and 95% confidence intervals. Continuously normally distributed variables were compared using t tests and reported as means with 95% confidence intervals while non–normally distributed data were compared using Wilcoxon rank sum tests and reported as medians and interquartile range (IQR).

The increase in creatinine from ICU admission to peak level was analyzed using generalized linear modeling, with results presented as least square means with 95% confidence intervals. Acute kidney injury (defined by RIFLE injury and failure class) and the need for RRT were analyzed using logistic regression with results reported as odds ratios (ORs) with 95% confidence intervals. Time-to-event analysis was performed using Cox proportional hazard modeling with results reported as hazard ratios (HRs) with 95% confidence intervals and presented as Kaplan-Meier curves. Comparisons between survival curves were performed using log-rank tests.

Multivariable sensitivity analysis was performed on all outcomes, adjusting for the a priori–defined covariates of sex, APACHE III score, diagnosis, operative status, and admission type (elective or emergency). Because the magnitude of the increase in creatinine level was dependent on the starting level, baseline creatinine level was also included as a covariate for all outcomes.

To explore the biological plausibility of our findings, we assessed the relationship between chloride intake and

changes in serum creatinine level in a nested cohort of 100 patients during each period in which detailed fluid data were obtained (eTable 1 and eTable 2 at http://www.jama.com). To further assess the possible relationship between markers of chloride intake and outcome, we conducted subgroup analyses according to time in ICU, APACHE score, risk of death, presence of sepsis, and cardiac surgery. To increase the robustness of reported findings, we assessed all outcome variables after excluding patients in whom baseline creatinine level was not known. In addition, to reduce the chance of a type I error due to reporting multiple outcomes, a 2-sided P value of .01 was used to indicate statistical significance.

RESULTS

During the study period, there were 1644 ICU admissions in 1533 patients (760 during the control period and 773 during the intervention period) with a median follow-up time of 11 days (IQR, 7-21 days) vs 11 days (7-22 days), respectively. The baseline characteristics of the patients admitted during the control and the intervention periods appear in TABLE 1. There were no significant differences with regard to age, sex, baseline creatinine level, APACHE scores, SAPS II, comorbidities, diagnostic groups, and types of admission. During the control period, 104 patients (13.7%; 95% CI, 11.3%-16.1%) did not have a baseline creatinine level available and had their baseline GFR estimated with the MDRD equation compared with 110 patients (14.2%; 95% CI, 11.7%-16.7%) during the intervention period (P=.46).

The detailed composition of study fluids appears in TABLE 2. The intervention period was associated with changes in fluid therapy. Saline prescription decreased from 2411 L to 52 L (3.2 vs 0.06 L/patient; P<.001) and 4% gelatin solution from 538 L to 0 L (0.7 vs 0 L/patient; P<.001). In contrast, administration of Hartmann solution increased from 469 L to 3205 L (0.6 vs 4.1 L/patient; P<.001), and Plasma-Lyte 148 from 65 L to 160 L (0.08 vs 0.2 L/patient; P=.04). In parallel, use of 4% albumin decreased from 269 L to 80 L (0.35 vs 0.1 L/patient; P<.001) and use of chloride-poor 20% albumin increased from 87 L to 268 L (0.1 vs 0.35 L/patient; P<.001).

The intervention period was associated with a decrease in solute therapy. Chloride administration decreased by a total of 144 504 mmol from 694 to 496 mmol/patient and study fluid–related sodium administration also decreased from 750 to 623 mmol/patient. However, study fluid–related potassium administration increased from 3.5 to 22 mmol/patient and lactate administration from 18 to 120 mmol/patient. Detailed fluid intake data in a nested cohort of 100 patients during each period are presented in eTable 2.

The chloride-restrictive strategy was associated with a significantly lower increase in serum creatinine level during ICU stay of 14.8 μmol/L (95% CI, 9.8-19.9 μmol/L) during the intervention period vs 22.6 μmol/L (95% CI, 17.5-27.7 μmol/L) during the control period (P=.03; adjusted P=.007). The increase in serum creatinine level during ICU stay was correlated with log-

Table 1. Baseline Characteristics of the Patients During the Control and Intervention Periods

	No. (%) [95% CI] of Patients[a]		
	Control Period (n = 760)	Intervention Period (n = 773)	P Value
Male sex	461 (61) [57-64]	483 (62) [59-66]	.46
Mechanical ventilation	498 (66) [62-69]	517 (67) [63-70]	.57
Admission after elective surgery	224 (29) [22-33]	232 (30) [27-33]	.82
Postoperative admission	377 (50) [46-53]	382 (49) [46-53]	.94
Admission from			
Emergency department	178 (23) [20-26]	168 (22) [19-25]	.43
Ward	129 (17) [14-20]	129 (17) [14-19]	.88
Admission for other ICU	76 (10) [8-12]	94 (12) [10-15]	.18
Diagnosis[b]			
Cardiovascular	294 (39) [35-42]	281 (36) [33-40]	.35
Gastrointestinal	126 (17) [14-19]	126 (16) [14-19]	.88
Metabolic	53 (7) [5.1-8.8]	34 (4.4) [2.9-5.9]	.03
Neurological	47 (6.2) [4.4-7.9]	68 (8.8) [6.8-11.0]	.05
Renal or genitourinary	26 (3.4) [2.1-4.7]	21 (2.7) [1.5-3.9]	.42
Respiratory	107 (14) [12-17]	111 (14) [12-17]	.87
Comorbidities[b]			
Severe sepsis or septic shock	55 (7.2) [5.4-9.0]	75 (10.0) [7.6-12.0]	.08
Chronic lung disease	18 (2.4) [1.3-3.5]	15 (1.9) [0.9-2.9]	.56
Chronic cardiovascular disease	19 (2.5) [1.4-3.6]	32 (4.1) [2.7-5.6]	.07
Chronic liver disease	50 (6.6) [4.8-8.4]	37 (4.8) [3.2-6.3]	.13
Chronic renal failure	34 (4.5) [3.6-5.4]	29 (3.8) [2.4-5.1]	.48
Immunosuppression	29 (3.8) [2.4-5.2]	26 (3.4) [2.1-4.7]	.63
Lymphoma	5 (0.7) [0.1-1.2]	5 (0.6) [0.1-1.2]	.98
Metastatic cancer	19 (2.5) [1.4-3.6]	22 (2.8) [1.6-4.0]	.67
Leukemia or myeloma	7 (0.9) [0.2-1.6]	14 (1.8) [0.8-2.8]	.13
	Mean (95% CI)		
Age, y	60 (59.0-61.6)	60.5 (59.2-61.8)	.86
APACHE II score (range: 0-71)[c]	15.8 (15.2-16.4)	16.0 (15.4-16.6)	.63
APACHE III score (range: 0-300)[c]	58 (56-60)	58 (56-60)	>.99
SAPS II (range: 0-163)[c]	32.4 (31.2-33.6)	32.4 (31.2-33.6)	.94
Baseline creatinine level, μmol/L	90 (69-125)	86 (67-121)	.07

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score.
SI conversion factor: To convert creatinine to mg/dL, divide by 88.4.
[a] The control period was from February 18 through August 17, 2008, and the intervention period was from February 18 through August 17, 2009.
[b] According to APACHE classification.
[c] Higher scores indicate greater illness severity.

chloride intake in the 200 patients in which detailed data were obtained (eFigure 1).

The chloride-restrictive intravenous strategy intervention period was associated with a decrease in the incidence of injury and failure class of RIFLE-defined AKI (**TABLE 3**). It was further associated with a decrease in RRT use for 78 patients (10%; 95% CI, 8.1%-12%) during the control period vs 49 patients (6.3%; 95% CI, 4.6%-8.1%) during the intervention period ($P=.005$). This decrease was a deviation from secular trends for the study ICU and consistent with changes in serum creatinine over time (eTable 3 and eFigure 2).

After adjusting for sex, APACHE III score, diagnosis, operative status, baseline serum creatinine level, and admission type (elective or emergency), the overall incidence of injury and failure class of RIFLE-defined AKI (OR, 0.52 [95% CI, 0.37-0.75]; $P<.001$) and the use of RRT (OR, 0.52 [95% CI, 0.33-0.81]; $P=.004$) remained significantly lower during the intervention period.

Significant differences by log-rank test were evident in time-to-first event curves of injury and failure class of RIFLE-defined AKI ($P<.001$; **FIGURE 1**) and RRT use ($P=.004$; **FIGURE 2**).

There were also significant differences in the HRs for these events after the Cox proportional hazards model adjustment. There was a HR of 0.52 (95% CI, 0.38-0.72; $P<.001$) for the development of injury and failure class of RIFLE-defined AKI and an HR of 0.52 (95% CI, 0.35-0.76; $P<.001$) for RRT use.

Subgroup analysis is shown in the eTable 4 and eFigure 3. Analysis after exclusion of patients for whom baseline serum creatinine level was not available did not alter the associations found (eSupplement).

Sixty-five patients (9%; 95% CI, 7%-11%) died in the ICU during the control period compared with 59 patients (8%; 95% CI, 6%-10%) during the intervention period ($P=.42$). Hospital mortality was 112 patients (15%; 95%

Table 2. Composition of Trial Fluids[a]

	0.9% Saline	Hartmann	4% Gelatin	Plasma-Lyte 148	Albumin	
					4%	20%
Sodium	150	129	154	140	140	48-100
Potassium	0	5	0	5	0	0
Chloride	150	109	120	98	128	19
Calcium	0	2	0	0	0	0
Magnesium	0	0	0	1.5	0	0
Lactate	0	29	0	0	0	0
Acetate	0	0	0	27	0	0
Gluconate	0	0	0	23	0	0
Octanoate	0	0	0	0	6.4	32

[a] All concentrations in mmol/L.

Table 3. Incidence of Acute Kidney Injury Stratified by Risk, Injury, Failure, Loss, and End-Stage (RIFLE) Serum Creatinine Criteria

	No. (%) [95% CI] of Patients[a]		
	Control Period (n = 760)	Intervention Period (n = 773)	P Value
RIFLE class			
Risk	71 (9.0) [7.2-11.0]	57 (7.4) [5.5-9.0]	.16
Injury	48 (6.3) [4.5-8.1]	23 (3.0) [1.8-4.2]	.002
Failure	57 (7.5) [5.6-9.0]	42 (5.4) [3.8-7.1]	.10
Injury and failure	105 (14) [11-16]	65 (8.4) [6.4-10.0]	<.001

[a] The control period was from February 18 through August 17, 2008, and the intervention period was from February 18 through August 17, 2009.

CI, 12%-17%) during the control period vs 102 patients (13%; 95% CI, 11%-16%) during the intervention period ($P=.44$); median ICU length of stay was 42.9 hours (IQR, 21.1-88.6 hours) vs 42.8 hours (IQR, 21.8-90.5 hours), respectively ($P=.52$); and median hospital length of stay was 11 days (IQR, 7-21 days) vs 11 days (IQR, 7-22 days) ($P=.57$). Of the patients who survived to ICU discharge after being treated with RRT, 6 patients (12%; 95% CI, 3%-21%) were still on dialysis at 3 months after discharge from the ICU during the control period compared with 5 patients (15%; 95% CI, 3%-27%) during the intervention period ($P=.95$). Thus, there were no differences in long-term dialysis requirements and in non–renal medium-term outcomes.

COMMENT

We performed a controlled before-and-after study to compare the renal functional changes associated with a chloride-restrictive intravenous strategy with those observed with a chloride-liberal intravenous fluid strategy. We found that a chloride-restrictive intravenous fluid strategy was associated with a significant reduction in the increase of mean creatinine level from baseline to peak ICU level. In addition, we found that such a strategy was associated with a significant decrease in the incidence of AKI and the use of RRT. Moreover, these findings remained significant after adjustment for baseline variables, were supported by a subgroup analysis (eTable 4) and a detailed nested cohort analysis (eTable 2), and were confirmed by time-to-first event curves and a proportional hazard analysis.

Comparison With Previous Studies

To our knowledge, no studies have assessed the renal effects of a chloride-restrictive intravenous fluid strategy applied to critically ill patients over days to weeks of ICU stay. However, our findings are in keeping with earlier observations in animal and human studies that suggest that solutions with supraphysi-

ological concentrations of chloride may have detrimental renal effects.[9-12] Our findings suggest that the shorter time to micturition,[11] greater urine output,[12] and better renal cortical perfusion[13] seen in previous controlled human studies may reflect clinically significant renal effects of chloride-containing intravenous fluids rather than minor fluctuation in osmolar control.[21] This notion is further supported by recent observational evidence in more than 30 000 surgical patients that saline therapy increases the risk of patients requiring acute dialysis compared with Plasma-Lyte administration.[22]

A possible explanation for these putative chloride-associated detrimental renal outcomes is provided by the renal vasoconstrictive effect of tubular chloride reabsorption, an effect reported in an earlier animal study.[9] In addition, greater chloride delivery to the macula densa may activate the tubuloglomerular feedback, a physiological process that regulates GFR. The tubuloglomerular feedback may trigger afferent arteriolar vasoconstriction, mesangial contraction, and associated reductions in GFR.[23-25] Furthermore, chloride infusion may induce thromboxane release with associated vaso-

constriction,[10] as well as an enhanced responsiveness to vasoconstrictor agents, particularly angiotensin II receptor blockers.[26] In this pragmatic clinical study, we were unable to dissect which of these mechanisms, if any, may have contributed to the clinical changes observed.

This was a bundle-of-care study. The control bundle of care was based on the delivery of commonly used chloride-rich fluids, while the interventional bundle of care was based on the removal of such fluids and the exclusive administration of lower chloride fluids. Thus, we are not in a position to identify which component of our intervention (restricting chloride, using balanced solutions containing lactate, stopping a commercial 4% gelatin solution, using more 20% albumin and less 4% albumin, giving less sodium, delivering more potassium, or any combination of these) might have been responsible for the changes in outcomes observed. To our knowledge, when comparing saline with balanced solutions, there is no way of distinguishing whether any differential clinical effect might be dependent on removing chloride, using a solution containing lactate, or other buffers, or both.

Removing a gelatin solution alone may have been responsible for our findings. We identified only 2 randomized controlled studies of gelatin solutions in critically ill patients reporting renal outcomes.[27,28] One found that the incidence of AKI was significantly lower with a gelatin solution compared with a starch solution.[27] The other compared a gelatin solution with 4.5% albumin and found no difference in the incidence of acute renal failure.[28] A recent meta-analysis found that gelatin solutions actually decreased the risk of AKI (OR, 0.43).[29]

The reduction in the use of 4% albumin may have been responsible for our findings. However, there are no studies to suggest that 4% albumin may decrease the risk of AKI. Resuscitation with 4% albumin was compared with saline in the Saline versus Albu-

Figure 1. Development of Stage 2 or 3 Acute Kidney Injury (AKI) While in the Intensive Care Unit (ICU)

No. at risk				
2008	761	225	98	56
2009	772	280	134	74
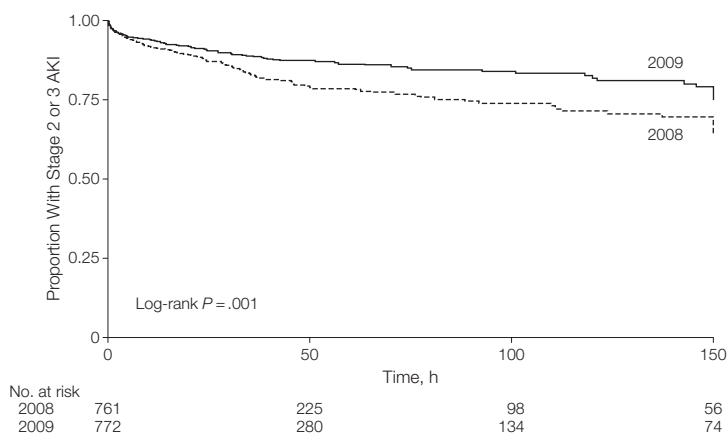
Stage 2 or 3 defined according to the Kidney Disease: Improving Global Outcomes clinical practice guideline.

Figure 2. Renal Replacement Therapy (RRT) in the Intensive Care Unit (ICU)

No. at risk				
2008	761	262	118	71
2009	772	303	150	83
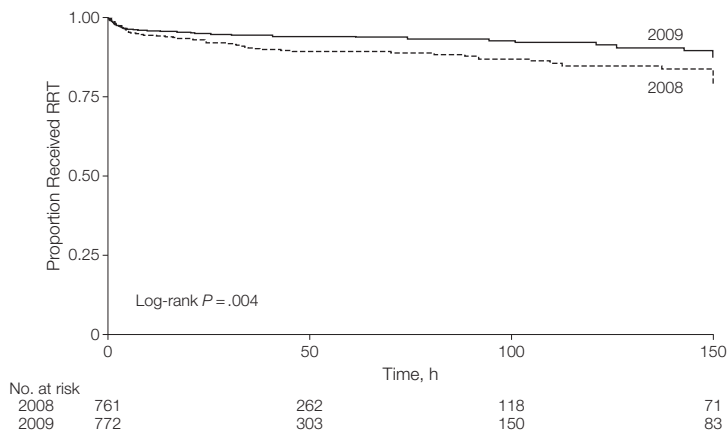
min Fluid Evaluation (SAFE) trial and no differences in renal outcomes were found.[30] The greater use of 20% albumin during the intervention period might explain our findings. However, the opposite might be expected to happen on physiological grounds. For example, classic Guytonian physiological studies demonstrate that hyperoncotic albumin increases renin secretion, markedly decreases urine flow rate and electrolyte excretion, and leads to either no change or a small decrease in GFR.[31] Moreover, an international prospective cohort study of more than 1000 ICU patients found that after adjustment for confounding factors and propensity score, the use of hyperoncotic albumin was associated with an OR of 5.99 for the occurrence of a renal event (either doubling of serum creatinine level or need for dialysis),[32] leading to consensus recommendations that hyperoncotic solutions be avoided.[33] However, other reports have contradicted such findings.[34,35] Thus, the effect of 20% albumin on the kidney remains unclear. In addition, and of great importance given recent findings,[36] no starch solution was administered to any patients during the study.

Significance of Study Findings

The findings of this study show that a chloride-restrictive intravenous strategy is associated with a decrease in the incidence of the more severe stages of AKI and the use of RRT. These findings, together with the previously reported observations that a chloride-liberal intravenous strategy can be associated with higher cost,[6] and the easy availability of cheap alternatives suggest the need to exert prudence in the administration of fluids with supraphysiological concentrations of chloride, especially in critically ill patients with evidence of early acute renal dysfunction or at risk of acute dysfunction.

Strengths and Limitations

To our knowledge, this is the first study to compare the associated changes with a chloride-restrictive approach vs a chloride-liberal approach throughout

the entire ICU stay. Our analysis of AKI incidence used the consensus RIFLE criteria and showed significant differences in AKI severity. The observations that the change in serum creatinine level was attenuated and that the use of RRT also decreased significantly during the intervention period add weight to the clinical implications of our observations.

The main limitation of our study is that it was not a blinded randomized trial. Unfortunately, it is practically impossible to blind a bundle of care involving at least 6 different types of fluid, packaged in different ways from polyvinyl chloride to glass, with different labels, and containers of different size. Thus, the unblinded nature of our study is similar to that of other before-and-after bundle-of-care studies involving complex care in acutely ill patients.[37,38] However, our sample size is large, there were no significant differences in the baseline characteristics between the patients during the control and the intervention periods, the renal outcomes remained significant after adjustment for baseline characteristics, and the study was executed in the same ICU in the absence of other changes to patient care. Additionally, the 2 study periods enrolled patients during the same time of the year, ruling out a seasonal effect.

The findings of a study with a before-and-after design are often subject to secular changes, which may have led to independent improvements in care. However, in our ICU, in the period before the intervention (from 2006 to 2008), there had been secular trends with a greater use of RRT and stable APACHE III scores (eTable 3). We did not collect information on the administration of chloride-rich fluid before or after ICU treatment. However, this was a study to test whether a chloride-restrictive approach (when used in an ICU) was associated with different renal outcomes in an ICU.

There are potential risks associated with restricting chloride-rich fluids and more isotonic fluids in patients with hyponatremia, alkalemia, cerebral edema, or traumatic brain injury. Such con-

siderations are important and are also the reason why some saline was prescribed during the intervention period to selected patients.

Assessment for baseline renal function is problematic and of limited accuracy if no preadmission information is available. In some patients, such information was absent and assessment of likely premorbid creatinine levels was achieved using the MDRD equation. This method has serious limitations. However, it was applied to an equal number of patients in each group and inaccuracies arising from its use are unlikely to have biased our results. Moreover, after excluding all patients in whom the MDRD equation was used, the results remained unchanged (eSupplement). We did not assess changes in novel biomarkers of renal injury.[39] However, their clinical value remains unclear and serum creatinine level is still the biomarker of choice in clinical care. Our follow-up data do not suggest long-term associations between chloride restriction and outcomes. This may reassure clinicians who use chloride-rich fluids. However, it may represent a type II error or the salvage effect of continuous RRT use. Further investigations of chloride restriction are needed to define the long-term consequences of this type of intervention. In addition, the outcomes were objective and dependent on laboratory tests, which were not amenable to ascertainment bias or manipulation.

Future Studies

Our findings need to be confirmed in different health care systems and different ICUs. Current knowledge on chloride and its effect on renal function is limited and relies on a number of assumptions.[8] More studies (both at basic science and clinical levels) must be undertaken to gain better insight into the renal effects of chloride.

CONCLUSIONS

We conducted a before-and-after study comparing a chloride-restrictive intra-

venous fluids strategy with a chloride-liberal intravenous fluids strategy in a multidisciplinary tertiary ICU. We found that restricting intravenous chloride intake was associated with a significant decrease in the incidence of AKI and the use of RRT. These observations support the desirability of further clinical studies in this field.

REFERENCES

1. McIntyre LA, Hébert PC, Fergusson D, Cook DJ, Aziz A; Canadian Critical Care Trials Group. A survey of Canadian intensivists' resuscitation practices in early septic shock. *Crit Care*. 2007;11(4):R74.
2. Finfer S, Liu B, Taylor C, et al; SAFE TRIPS Investigators. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. *Crit Care*. 2010;14(5):R185.
3. Wakim KG. "Normal" 0.9 per cent salt solution is neither "normal" nor physiological. *JAMA*. 1970; 214(9):1710.
4. Oliveira RP, Velasco I, Soriano FG, Friedman G. Clinical review: hypertonic saline resuscitation in sepsis. *Crit Care*. 2002;6(5):418-423.
5. Wan L, Bellomo R, May CN. Bolus hypertonic or normal saline resuscitation in gram-negative sepsis: systemic and regional haemodynamic effects in sheep. *Crit Care Resusc*. 2011;13(4):262-270.
6. Yunos NM, Kim IB, Bellomo R, et al. The biochemical effects of restricting chloride-rich fluids in intensive care. *Crit Care Med*. 2011;39(11):2419-2424.
7. Smith RJ, Reid DA, Delaney EF, Santamaria JD. Fluid therapy using a balanced crystalloid solution and acid-base stability after cardiac surgery. *Crit Care Resusc*. 2010;12(4):235-241.
8. Yunos NM, Bellomo R, Story D, Kellum J. Bench-to-bedside review: chloride in critical illness. *Crit Care*. 2010;14(4):226.
9. Wilcox CS. Regulation of renal blood flow by plasma chloride. *J Clin Invest*. 1983;71(3):726-735.
10. Bullivant EMA, Wilcox CS, Welch WJ. Intrarenal vasoconstriction during hyperchloremia: role of thromboxane. *Am J Physiol*. 1989;256(1 pt 2): F152-F157.
11. Williams EL, Hildebrand KL, McCormick SA, Bedel MJ. The effect of intravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. *Anesth Analg*. 1999; 88(5):999-1003.
12. Wilkes NJ, Woolf R, Mutch M, et al. The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. *Anesth Analg*. 2001;93(4):811-816.
13. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and Plasma-Lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg*. 2012;256(1):18-24.
14. Bagshaw SM, George C, Bellomo R; ANZICS Database Management Committee. Changes in the incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units. *Crit Care*. 2007;11(3):R68.

15. Srisawat N, Lawsin L, Uchino S, Bellomo R, Kellum JA; BEST Kidney Investigators. Cost of acute renal replacement therapy in the intensive care unit: results from the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study. *Crit Care*. 2010; 14(2):R46.
16. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8(4):R204-R212.
17. RENAL Study Investigators. Renal replacement therapy for acute kidney injury in Australian and New Zealand intensive care units: a practice survey. *Crit Care Resusc*. 2008;10(3):225-230.
18. Bellomo R, Cass A, Cole L, et al; RENAL Replacement Therapy Study Investigators. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med*. 2009;361(17):1627-1638.
19. Disease K. Improving global outcomes clinical practice guidelines: definition and classification of acute kidney injury. *Kidney Int Suppl*. 2012;2(suppl 1): 19-36.
20. Závada J, Hoste E, Cartin-Ceba R, et al; AKI6 investigators. A comparison of three methods to estimate baseline creatinine for RIFLE classification. *Nephrol Dial Transplant*. 2010;25(12):3911-3918.
21. Guidet B, Soni N, Della Rocca G, et al. A balanced view of balanced solutions. *Crit Care*. 2010; 14(5):325.
22. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. *Ann Surg*. 2012;255(5): 821-829.
23. Schnermann J, Ploth DW, Hermle M. Activation of tubulo-glomerular feedback by chloride transport. *Pflugers Arch*. 1976;362(3):229-240.
24. Salomonsson M, Gonzalez E, Kornfeld M, Persson AE. The cytosolic chloride concentration in macula densa and cortical thick ascending limb cells. *Acta Physiol Scand*. 1993;147(3):305-313.
25. Hashimoto S, Kawata T, Schnermann J, Koike T. Chloride channel blockade attenuates the effect of angiotensin II on tubuloglomerular feedback in WKY but not spontaneously hypertensive rats. *Kidney Blood Press Res*. 2004;27(1):35-42.
26. Quilley CP, Lin YS, McGiff JC. Chloride anion concentration as a determinant of renal vascular responsiveness to vasoconstrictor agents. *Br J Pharmacol*. 1993;108(1):106-110.
27. Schortgen F, Lacherade JC, Bruneel F, et al. Effects of hydroxyethylstarch and gelatin on renal func-

tion in severe sepsis: a multicentre randomised study. *Lancet*. 2001;357(9260):911-916.
28. Stockwell MA, Scott A, Day A, Riley B, Soni N. Colloid solutions in the critically ill: a randomised comparison of albumin and polygeline 2: serum albumin concentration and incidences of pulmonary oedema and acute renal failure. *Anaesthesia*. 1992;47(1): 7-9.
29. Saw MM, Chandler B, Ho KM. Benefits and risks of using gelatin solution as a plasma expander for perioperative and critically ill patients: a meta-analysis. *Anaesth Intensive Care*. 2012;40(1):17-32.
30. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R; SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350(22): 2247-2256.
31. Hall JE, Guyton AC. Changes in renal hemodynamics and renin release caused by increased plasma oncotic pressure. *Am J Physiol*. 1976;231(5 pt 1): 1550-1556.
32. Schortgen F, Girou E, Deye N, Brochard L; CRYCO Study Group. The risk associated with hyperoncotic colloids in patients with shock. *Intensive Care Med*. 2008;34(12):2157-2168.
33. Brochard L, Abroug F, Brenner M, et al; ATS/ERS/ESICM/SCCM/SRLF Ad Hoc Committee on Acute Renal Failure. An official ATS/ERS/ESICM/SCCM/SRLF statement: prevention and management of acute renal failure in the ICU patient: an international consensus conference in intensive care medicine. *Am J Respir Crit Care Med*. 2010;181(10):1128-1155.
34. Wiedermann CJ, Dunzendorfer S, Gaioni LU, Zaraca F, Joannidis M. Hyperoncotic colloids and acute kidney injury: a meta-analysis of randomized trials. *Crit Care*. 2010;14(5):R191.
35. Jacob M, Chappell D, Conzen P, Wilkes MM, Becker BF, Rehm M. Small-volume resuscitation with hyperoncotic albumin: a systematic review of randomized clinical trials. *Crit Care*. 2008;12(2):R34.
36. Perner A, Haase N, Guttormsen AB, et al; 6S Trial Group; Scandinavian Critical Care Trials Group. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367(2):124-134.
37. Sharek PJ, Parast LM, Leong K, et al. Effect of a rapid response team on hospital-wide mortality and code rates outside the ICU in a Children's Hospital. *JAMA*. 2007;298(19):2267-2274.
38. Chan PS, Khalid A, Longmore LS, Berg RA, Kosiborod M, Spertus JA. Hospital-wide code rates and mortality before and after implementation of a rapid response team. *JAMA*. 2008;300(21):2506-2513.
39. Bagshaw SM. Subclinical acute kidney injury: a novel biomarker-defined syndrome. *Crit Care Resusc*. 2011;13(3):201-203.