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Balanced Crystalloids versus Saline in Critically Ill Adults with Hyperkalemia or Acute Kidney Injury: Secondary Analysis of a Clinical Trial

To the Editor:

Hyperkalemia is common in critically ill patients and is associated with an increased risk of cardiac arrhythmia, cardiac arrest, and death (1). Intravenous fluids affect plasma electrolyte concentrations (2). Saline (0.9% sodium chloride) causes hyperchloremia and metabolic acidosis, which may move potassium from the intracellular space into the interstitial fluid and plasma (3). Balanced crystalloids, such as lactated Ringer's solution or Plasma-Lyte A, contain 4.0–5.0 mmol/L of potassium—a concentration similar to that of normal human plasma. The theoretical risk of hyperkalemia from supplemental potassium is a frequently cited concern with balanced crystalloids (4). However, balanced crystalloids also contain buffers such as lactate and acetate, which may prevent acidosis-induced potassium shifts (3). To evaluate the effect of fluid composition on the incidence of hyperkalemia and renal replacement therapy (RRT), we performed a secondary analysis of a large, pragmatic trial comparing balanced crystalloids with saline among critically ill adults (2).

Some of the results of this study have been previously reported in the form of an abstract (5).

Methods

Patient populations. SMART (Isotonic Solutions and Major Adverse Renal Events Trial) compared balanced crystalloids versus saline among 15,802 critically ill adults (2). We identified the following two cohorts of patients in SMART at risk of severe hyperkalemia: patients with hyperkalemia at ICU admission and patients with acute kidney injury (AKI) at ICU admission. Hyperkalemia at baseline was defined

as a plasma potassium concentration of ≥ 6.5 mmol/L in the 24 hours before ICU admission (or in the 6 h after ICU admission if no potassium values were available before ICU admission). A potassium concentration of ≥ 6.5 mmol/L was used to define hyperkalemia in the original SMART and other prior trials of balanced crystalloids (2, 6). AKI at baseline was defined as a plasma creatinine concentration in the 24 hours before ICU admission (or in the 6 h after ICU admission if no creatinine values were available before ICU admission) meeting criteria for stage 2 or greater kidney injury according to the Kidney Disease: Improving Global Outcomes creatinine criteria (7). The method for identifying baseline creatinine and calculating a value when a measured value was unavailable has been previously described (2).

Study outcomes. Outcomes included severe hyperkalemia, defined as a plasma potassium concentration ≥ 7.0 mmol/L (8), between ICU admission and hospital discharge; highest potassium concentration from ICU admission to hospital discharge; death; new receipt of RRT; and incident AKI by the Kidney Disease: Improving Global Outcomes creatinine criteria. All outcomes were censored at the first of hospital discharge or 30 days. Patients who had received RRT before ICU admission were ineligible to meet criteria for incident AKI or new receipt of RRT but were eligible for other outcomes.

Statistical analysis. Analyses used the same approach to modeling as the original SMART (2). Binary outcomes were analyzed with a generalized, linear, mixed-effects model that included group assignment as a fixed effect and the ICU to which the patient was admitted as a random effect. Continuous outcomes were analyzed using a proportional odds logistic regression model that included group assignment as an independent variable and used robust covariance matrix estimates to adjust for within-ICU correlation. For outcomes that included potassium, models included baseline potassium as a fixed effect.

Results

A total of 254 patients had a baseline potassium concentration of ≥ 6.5 mmol/L, of whom 67 were excluded for artifactual hyperkalemia from hemolysis, and 187 were included in the analysis (94 in the balanced crystalloids group and 93 in the saline group). Among 15,016 patients in SMART who had not received RRT before ICU admission, 1,324 patients had AKI at baseline (681 in the balanced crystalloid group and 643 in the saline group). The characteristics of patients randomized to the balanced crystalloid and saline groups in each cohort are displayed in Table 1.

Among patients with hyperkalemia at baseline, eight patients (8.5%) in the balanced crystalloid group and 13 patients (14.0%) in the saline group went on to experience severe hyperkalemia (adjusted odds ratio, 0.57; 95% confidence interval [CI], 0.22–1.46; $P = 0.24$) (Figure 1 and Table 1). New or worsening AKI (25.3% vs. 42.0%; adjusted odds ratio, 0.47; 95% CI, 0.23–0.94; $P = 0.03$) and new receipt of RRT (13.9% vs. 29.0%; adjusted odds ratio, 0.40; 95% CI, 0.17–0.90; $P = 0.03$) occurred less frequently in patients in the balanced crystalloid group compared with those in the saline group (Figure 1 and Table 1). The receipt of potassium-lowering therapies, including sodium polystyrene, insulin/dextrose, sodium bicarbonate, and calcium gluconate/chloride, was similar between the two groups (Table 1).

Among patients with AKI at baseline, three patients (0.4%) in the balanced crystalloid group and nine patients (1.4%) in the saline group experienced severe hyperkalemia (adjusted odds ratio, 0.33; 95% CI, 0.09–1.25; $P = 0.10$) (Figure 1 and Table 1). A total of 97 patients (14.2%) in the balanced crystalloid group received new RRT

Table 1. Patient Characteristics, Volume of Isotonic Crystalloid, and Outcomes

Patient Characteristics	Hyperkalemia at Enrollment			AKI at Enrollment		
	Balanced (n = 94)	Saline (n = 93)	P Value	Balanced (n = 681)	Saline (n = 643)	P Value
Baseline characteristics						
Age, yr	60 (43.0–70.0)	55 (44.0–65.0)	0.21	59 (45–69)	60 (49–69)	0.51
Sex, M, n (%)	58 (61.7)	57 (61.3)	0.95	407 (59.8)	387 (60.2)	0.88
Race, white, n (%)	74 (78.7)	59 (63.4)	0.02	509 (74.7)	489 (76.0)	0.58
Weight, kg	79.8 (69.9–92.5)	77.1 (68.0–92.1)	0.53	82.6 (68.0–99.8)	82.1 (68.9–99.8)	0.85
CKD or prior RRT,* n (%)	54 (57.4)	50 (53.8)	0.61	107 (15.7)	106 (16.5)	0.70
CKD	39 (41.5)	26 (28.0)	0.05	107 (15.7)	106 (16.5)	0.70
Prior RRT	15 (16.0)	24 (25.8)	0.01	N/A[†]	N/A[†]	
Sepsis or septic shock, n (%)	27 (28.7)	23 (24.7)	0.54	250 (36.7)	270 (42.0)	0.05
Mechanical ventilation, n (%)	31 (33.0)	35 (37.6)	0.51	294 (43.2)	280 (43.5)	0.89
Vasopressors, n (%)	25 (26.6)	27 (29.0)	0.71	286 (42.0)	291 (45.3)	0.23
AKI, stage 2 or greater[‡§]	33 (41.8)	35 (50.7)	0.28	681 (100.0)	643 (100.0)	1.00
University Health Consortium expected mortality, mean ± SD, %[∥]	17.1 ± 26.2	17.7 ± 22.9	0.83	20.4 ± 25.0	21.1 ± 24.9	0.31
Potassium on ICU admission, mmol/L	7.0 (6.7–7.4)	7.0 (6.8–7.5)	0.61	4.5 (3.9–5.3)	4.5 (3.9–5.1)	0.27
Bicarbonate on ICU admission, mmol/L	16.0 (10.0–19.0)	16.5 (12.2–20.0)	0.22	19.0 (15.0–23.0)	19.0 (15.0–22.0)	0.87
Creatinine on ICU admission, mg/dl[‡]	3.3 (2.0–4.9)	2.7 (1.6–4.1)	0.29	2.5 (1.7–3.7)	2.4 (1.7–3.4)	0.52
Volume of intravenous fluid through Day 30[¶], mean ± SD, ml						
0.9% sodium chloride	1,917 ± 3,518	3,713 ± 5,741	<0.001	1,260 ± 3,362	3,148 ± 4,739	<0.001
Balanced crystalloid	2,608 ± 4,046	226 ± 855	<0.001	2,755 ± 4,113	654 ± 2,314	<0.001
Total isotonic crystalloid	4,524 ± 5,913	3,939 ± 5,858	0.82	4,015 ± 5,679	3,802 ± 5,570	0.12
Receipt of potassium-lowering treatments, n (%)						
Kayexalate	35 (37.2)	38 (40.9)	0.61	N/A**	N/A**	N/A
Sodium bicarbonate	26 (27.7)	31 (33.3)	0.4	N/A**	N/A**	N/A
Intravenous insulin	36 (38.3)	48 (51.6)	0.07	N/A**	N/A**	N/A
Clinical outcomes						
Severe hyperkalemia (K ≥ 7.0 mmol/L), n (%)	8 (8.5)	13 (14)	0.24	3 (0.4)	9 (1.4)	0.10
Highest potassium concentration, mmol/L	6.2 (5.3–6.8)	6.3 (5.5–6.9)	0.20	5.0 (4.4–5.7)	5.1 (4.5–5.7)	0.001
Lowest bicarbonate concentration, mmol/L	16.0 (12.0–20.0)	17.0 (13.0–20.0)	0.84	17.0 (14.0–20.0)	16.0 (13.0–19.0)	<0.001
Stage 2 or greater AKI developing after enrollment, n (%)[‡§]	20/79 (25.3)	29/69 (42.0)	0.03	304 (44.6)	332 (51.6)	0.01
New RRT, n (%)[‡]	11/79 (13.9)	20/69 (29.0)	0.03	97 (14.2)	125 (19.4)	0.01
In-hospital mortality, n (%)	17 (18.1)	18 (19.4)	0.82	188 (27.6)	180 (28.0)	0.88

Definition of abbreviations: AKI = acute kidney injury; CKD = chronic kidney disease (stage 3 or greater); N/A = not applicable; RRT = renal replacement therapy.

Continuous data are presented as median (25th percentile–75th percentile) unless otherwise noted.

*Chronic kidney disease stage 3 or greater is defined as a glomerular filtration rate of <60 ml/min per 1.73 m^2 as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation using the patient's baseline creatinine concentration.

[†]Patients who had received RRT before admission were excluded from the cohort of patients with AKI on admission.

[‡]Patients who had received RRT before ICU admission were excluded from calculations of AKI and creatinine at baseline and were ineligible to meet the clinical outcome criteria for new RRT or new AKI developing after enrollment.

[§]Stage 2 or greater AKI is defined using the Kidney Disease Improving Global Outcomes creatinine criteria (7) as any creatinine value between ICU admission and discharge or 30 days that is *1*) increased at least 0.3 mg/dl from a preceding post–ICU admission value and *2*) at least 200% of the baseline value, at least 200% of a preceding post–ICU admission value, or at least 4.0 mg/dl; or new receipt of RRT.

[∥]The University Health Consortium index is a severity-of-illness score calculated using variables available on hospital admission to provide an estimation of mortality from 0% to 100%.

[¶]Cumulative volume of fluid ordered from ICU admission through Day 30 includes fluid ordered both in the ICU and after transfer out of the ICU. Balanced crystalloid includes lactated Ringer's and Plasma-Lyte A.

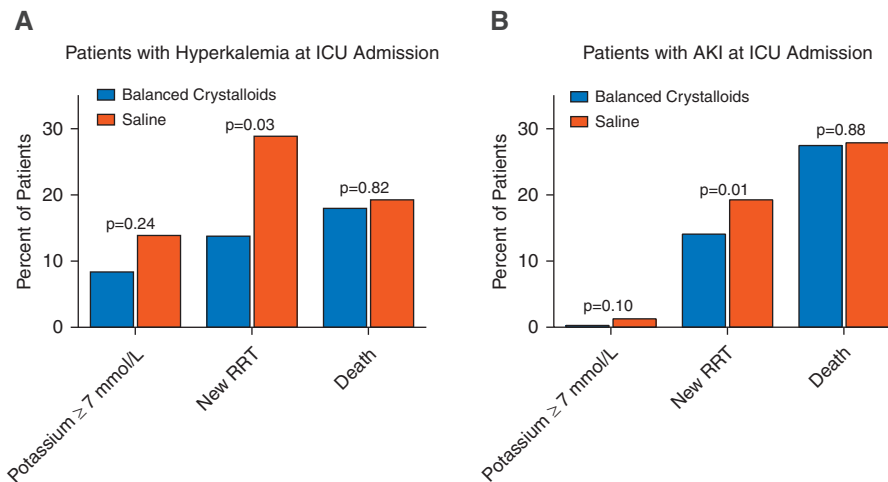**Data on potassium-lowering therapies only available among patients with hyperkalemia on ICU admission.

Figure 1. Incidence of severe hyperkalemia, receipt of new RRT, and death in the balanced crystalloid group versus saline group among patients with hyperkalemia at ICU admission (*A*) or AKI at ICU admission (*B*). Vertical bars represent the overall incidence of the designated outcome in each group. The *P* value represents the between-group difference in the designated outcome as calculated using a generalized, linear, mixed-effects model that included group assignment as a fixed effect and the ICU to which the patient was admitted as a random effect. For severe hyperkalemia, the model also included baseline potassium as a fixed effect. AKI = acute kidney injury; RRT = renal replacement therapy.

compared with 125 patients (19.4%) in the saline group (adjusted odds ratio, 0.69; 95% CI, 0.51–0.92; $P = 0.01$) (Figure 1 and Table 1).

Results were similar in sensitivity analyses that used alternative definitions of hyperkalemia at ICU admission. Of the 491 patients with a potassium concentration of ≥ 5.5 mmol/L in the balanced crystalloid group, a total of 23 (4.7%) experienced severe hyperkalemia, compared with 22 of 455 (4.8%) in the saline group. Of the 258 patients with a potassium concentration of ≥ 6.0 mmol/L in the balanced crystalloid group, a total of 16 (6.2%) experienced severe hyperkalemia, compared with 16 of 242 (6.6%) in the saline group.

Discussion

In this secondary analysis of a clinical trial, the use of balanced crystalloids was not associated with an increased incidence of severe hyperkalemia compared with saline and was associated with a significantly lower incidence of RRT among patients with hyperkalemia at ICU admission and patients with AKI at ICU admission. These results are consistent with randomized trials among patients undergoing renal transplantation, in whom the administration of balanced crystalloids resulted in similar or lower rates of hyperkalemia compared with saline (9).

Patients with hyperkalemia at ICU admission received a mean of approximately 4 L of isotonic crystalloid during their critical illness. This volume of balanced crystalloid solution contains 16–20 mmol of potassium, or approximately 0.5% of total body potassium for a 70-kg person (10). Our results suggest that the acid–base effects of isotonic crystalloids are more important for potassium homeostasis than the relatively small amount of potassium in these fluids.

Our study has several limitations, including conduct at a single center, lack of blinding, initiation of RRT at the discretion of the treating clinicians, and limited power for subgroup analyses among patients with hyperkalemia and AKI. Based on prior guidelines (8), our analysis defined severe hyperkalemia as a serum potassium ≥ 7.0 mmol/L, but there is no standard definition for severe hyperkalemia, and the threshold at which complications from hyperkalemia may occur is likely to vary on the basis of patient characteristics. Because the analysis focused on a subgroup of patients from SMART identified by laboratory values obtained after presentation, group assignment is not protected by randomization, and imbalances in baseline characteristics could contribute to observed differences in outcomes. However, baseline demographics, severity of illness, and potassium concentrations were similar between groups. Saline administration in the balanced crystalloid group was more common in this secondary analysis of patients with hyperkalemia than in SMART overall. Such crossover, however, would bias our results toward the null hypothesis and would not explain a numerically lower incidence of hyperkalemia and new RRT in the balanced crystalloid group.

In conclusion, in this secondary analysis of patients with hyperkalemia or AKI in a large randomized trial, use of balanced crystalloids was not associated with a higher incidence of severe hyperkalemia and appeared to be associated with a lower incidence of new RRT. ∎

Alexandra H. Toporek, M.D.*
Matthew W. Semler, M.D., M.Sc.*
Wesley H. Self, M.D., M.P.H.
Gordon R. Bernard, M.D.
Li Wang, M.S.
Edward D. Siew, M.D.
Joanna L. Stollings, Pharm.D.
Jonathan P. Wanderer, M.D., M.Phil., F.A.S.A., F.A.M.I.A.
Todd W. Rice, M.D., M.Sc.
Jonathan D. Casey, M.D., M.Sc.‡
Vanderbilt University Medical Center
Nashville, Tennessee

For the SMART Investigators and the Pragmatic Critical Care Research Group

ORCID IDs: 0000-0003-0902-0422 (A.H.T.); 0000-0002-7664-8263 (M.W.S.); 0000-0002-0977-290X (J.D.C.).

*These authors contributed equally to this work.
‡Corresponding author (e-mail: jonathan.d.casey@vumc.org).

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Sleep Apnea and Poor COVID-19 Outcomes: Beware of Causal Intermediates and Colliders

To the Editor:

We read with interest the report by Cade and colleagues on the association between obstructive sleep apnea (OSA) and adverse outcomes such as hospitalization and death among adults with coronavirus disease (COVID-19) (1). We commend the authors for asking this important research question and their thorough analysis. However, for each of the three outcomes that they investigated, the
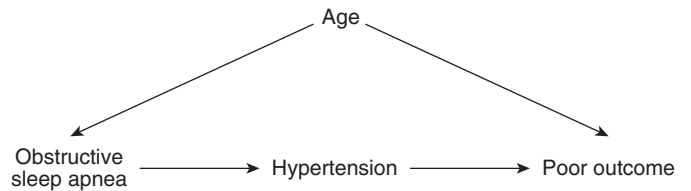
Figure 1. Directed acyclic graph for the effect of obstructive sleep apnea on poor outcome among patients with coronavirus disease (COVID-19). Age is a confounder of the association, whereas hypertension is a causal intermediate.

effect of OSA as measured by the odds ratio was progressively attenuated as additional variables were adjusted for. It is possible that a portion of this attenuation may be due to overadjustment bias (2).

Overadjustment bias occurs when a data analyst controls for an intermediate variable on the causal path from the exposure variable (e.g., OSA) to the outcome (e.g., hospitalization due to COVID-19) (2). Causal diagrams may be used to identify causal intermediates and hence avoid overadjustment bias (2, 3).
Figure 1 is a causal diagram known as a directed acyclic graph (DAG). In this simplified DAG from a hypothetical study, OSA is the exposure and the endpoint is poor outcome (PO), which represents the composite endpoint of inpatient admission, receipt of mechanical ventilation, or death. OSA may lead to hypertension, which in turn is a risk factor for a PO. Hypertension is a causal intermediate on the path between OSA and PO. According to this DAG, hypertension should not be adjusted for using stratification or other techniques such as multiple regression modeling. Controlling for (adjusting for) an intermediate will prevent the estimation of the total causal effect of OSA on PO (3).

In Figure 1, the data analyst believes the patient's age is a confounder of the association between OSA and PO. A confounder is a variable that is related to both the exposure and the outcome yet is not an effect of the exposure (4). When inspecting a DAG, a variable can be identified as a confounder of the association between the exposure and the outcome if it is a common cause of the exposure variable and the outcome (3). Confounders should be adjusted for.

An additional benefit of DAGs is the ability to identify colliders. A collider is a variable where two arrowheads meet (3). In other words, a collider is a variable that is in the middle of an inverted fork in a
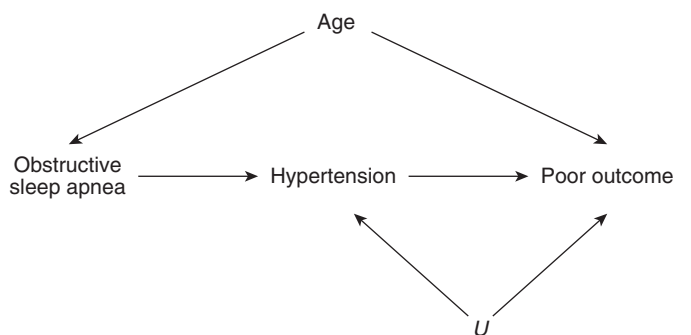

Figure 2. Directed acyclic graph for the effect of obstructive sleep apnea on poor outcome among patients with coronavirus disease (COVID-19). Hypertension is a collider on the path from obstructive sleep apnea to poor outcome. *U* is an unmeasured variable such as a medication or illness.