EDITORIAL

Patient-Centered Outcomes and Resuscitation Fluids

John Myburgh, M.D., Ph.D.

During the past 50 years, the use of intravenous resuscitation fluids in critically ill patients has been based on physiological principles rather than on evidence from clinical trials.[1] None of the current proprietary resuscitation fluids have been formally evaluated for safety and efficacy, and only a handful of the other drugs commonly used in acute care, such as vasopressors, antiarrhythmic drugs, and antibiotics, have been formally evaluated for efficacy and safety despite their established roles in clinical practice.

In the past decade, results from randomized, controlled trials have shown that the type of resuscitation fluid used in critically ill patients may adversely affect patient-centered outcomes. Colloids such as albumin are associated with increased mortality among patients with traumatic brain injury,[2] and hydroxyethyl starch is associated with acute kidney injury that has required renal-replacement therapy in some patients with severe sepsis.[3]

Consequently, in critically ill patients, crystalloids, particularly 0.9% sodium chloride (saline), have been preferred over semisynthetic colloids even though there is little evidence of the safety and efficacy of saline.[4] The use of saline, particularly in large volumes, is associated with the generation of a hyperchloremic metabolic acidosis that has in turn been associated with the development of acute kidney injury. Observational trials involving critically ill patients have shown reductions in acute kidney injury and lower mortality when crystalloids with a lower chloride concentration than saline — so-called buffered or balanced solutions — are used.[5-7]

None of the currently used balanced crystalloids, which include compound sodium lactate (lactated Ringer's solution) and solutions in which anions such as acetate, gluconate, or bicarbonate are substituted for lactate (e.g., Plasma-Lyte solutions), are truly buffered or balanced. These balanced crystalloid solutions are hypotonic relative to the extracellular fluid and are associated with the generation of a metabolic alkalosis. In addition, the excess effects of substituted anions, particularly acetate, may be associated with adverse effects.[8]

This issue of the *Journal* includes reports of the results of two pragmatic, multiple-crossover, randomized controlled trials from a single center that compare the effects of resuscitation with balanced crystalloids versus saline, primarily considering major adverse events affecting the kidney. In each trial, eligibility was defined by the location of hospital admission. Noncritically ill patients admitted from the emergency department to a hospital ward were assigned to the Saline against Lactated Ringer's or Plasma-Lyte in the Emergency Department (SALT-ED) trial.[9] Critically ill patients who were admitted from the emergency department, operating room, or general ward to an intensive care unit were referred to the Isotonic Solutions and Major Adverse Renal Events Trial (SMART).[10]

In the SALT-ED trial, the primary outcome was the number of hospital-free days at day 28, whereas in SMART, the primary outcome was determined by a composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction at 30 days (which was defined by changes in serum creatinine level). Patients in both trials received relatively modest volumes of either open-label balanced crystalloids (predominantly lactated Ringer's solution or, less frequently, Plasma-Lyte A) or open-label saline, prescribed by clinicians on a random basis in alternating months. In both trials, patients who received balanced crystalloids had

significantly lower concentrations of serum sodium and chloride and higher concentrations of bicarbonate at the end of treatment than those who received saline. The use of balanced crystalloids was associated with a significant reduction in the composite outcome of death from any cause, new renal-replacement therapy, or persistent renal dysfunction in both trials, largely as a result of reduced persistent acute kidney injury at day 30. No significant differences in short-term mortality or in the use of renal-replacement therapy were observed between the balanced-crystalloid and saline groups.

Caution is required in interpreting these results. The patient populations in these trials were categorized by hospital location, which may not relate to the acuity of illness or to the increased risk of adverse outcomes. Surrogate outcomes, such as short-term improvements in biochemical concentrations or physiological variables, may not translate into beneficial, patient-centered outcomes. Although composite outcomes are used to mitigate competing risks in trials with low event rates (which characterized these two trials), such scoring systems are prone to confounding, even after statistical adjustment. The composite outcome, in which death, renal-replacement therapy, and a doubling of creatinine level (subject to imputation bias) are treated as equivalent components, is a metric that is not applicable as a patient-centered outcome.

What clinicians need to consider is whether the results of an open-label trial conducted in a single, major U.S. medical center can be generalized to the ways in which their own patients survive, feel, and function. None of the currently used resuscitation fluids are "physiological," and questions regarding their safety and efficacy will remain, despite the results of these two trials and any randomized, controlled trials that are currently recruiting participants. Considerations remain regarding the effects of different types of resuscitation fluids and the ways they are used in specific, high-risk patient populations. Assessments of longer-term, patient-centered outcomes and health economics are fundamental to informing clinicians about their choice of resuscitation fluids in critically ill patients. The trials presented here inform that thinking but do not provide unequivocal clinical direction.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the University of New South Wales, the George Institute for Global Health, and St. George Hospital, Sydney.

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ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

Matthew W. Semler, M.D., Wesley H. Self, M.D., M.P.H., Jonathan P. Wanderer, M.D., Jesse M. Ehrenfeld, M.D., M.P.H., Li Wang, M.S., Daniel W. Byrne, M.S., Joanna L. Stollings, Pharm.D., Avinash B. Kumar, M.D., Christopher G. Hughes, M.D., Antonio Hernandez, M.D., Oscar D. Guillamondegui, M.D., M.P.H., Addison K. May, M.D., Liza Weavind, M.B., B.Ch., Jonathan D. Casey, M.D., Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D., and Todd W. Rice, M.D., for the SMART Investigators and the Pragmatic Critical Care Research Group*

ABSTRACT

BACKGROUND

Both balanced crystalloids and saline are used for intravenous fluid administration in critically ill adults, but it is not known which results in better clinical outcomes.

METHODS

In a pragmatic, cluster-randomized, multiple-crossover trial conducted in five intensive care units at an academic center, we assigned 15,802 adults to receive saline (0.9% sodium chloride) or balanced crystalloids (lactated Ringer's solution or Plasma-Lyte A) according to the randomization of the unit to which they were admitted. The primary outcome was a major adverse kidney event within 30 days — a composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction (defined as an elevation of the creatinine level to ≥200% of baseline) — all censored at hospital discharge or 30 days, whichever occurred first.

RESULTS

Among the 7942 patients in the balanced-crystalloids group, 1139 (14.3%) had a major adverse kidney event, as compared with 1211 of 7860 patients (15.4%) in the saline group (marginal odds ratio, 0.91; 95% confidence interval [CI], 0.84 to 0.99; conditional odds ratio, 0.90; 95% CI, 0.82 to 0.99; P=0.04). In-hospital mortality at 30 days was 10.3% in the balanced-crystalloids group and 11.1% in the saline group (P=0.06). The incidence of new renal-replacement therapy was 2.5% and 2.9%, respectively (P=0.08), and the incidence of persistent renal dysfunction was 6.4% and 6.6%, respectively (P=0.60).

CONCLUSIONS

Among critically ill adults, the use of balanced crystalloids for intravenous fluid administration resulted in a lower rate of the composite outcome of death from any cause, new renal-replacement therapy, or persistent renal dysfunction than the use of saline. (Funded by the Vanderbilt Institute for Clinical and Translational Research and others; SMART-MED and SMART-SURG ClinicalTrials.gov numbers, NCT02444988 and NCT02547779.)

From the Department of Medicine, Division of Allergy, Pulmonary, and Critical Care Medicine (M.W.S., J.D.C., G.R.B., T.W.R.), the Departments of Emergency Medicine (W.H.S.), Anesthesiology (J.P.W., J.M.E., A.B.K., C.G.H., A.H., L. Weavind, A.D.S.), Biomedical Informatics (J.P.W., J.M.E.), Surgery (J.M.E., O.D.G., A.K.M.), Health Policy (J.M.E.), Biostatistics (L. Wang, D.W.B.), and Pharmaceutical Services (J.L.S.), and the Division of Nephrology and Hypertension, Vanderbilt Center for Kidney Disease and Integrated Program for Acute Kidney Disease (E.D.S.) — all at Vanderbilt University Medical Center, Nashville. Address reprint requests to Dr. Rice at the Department of Medicine, Vanderbilt University Medical Center, T-1218 MCN, 1161 21st Ave. S., Nashville, TN 37232, or at todd.rice@vanderbilt.edu.

*A complete list of the SMART Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Intravenous crystalloid solutions are commonly administered in critical care, yet the question of whether crystalloid composition affects patient outcomes remains unanswered.[1] Historically, 0.9% sodium chloride (saline) has been the most commonly administered intravenous fluid.[2,3] Data suggest that intravenous saline may be associated with hyperchloremic metabolic acidosis,[4] acute kidney injury,[5] and death.[6,7] Crystalloid solutions with electrolyte compositions closer to that of plasma (balanced crystalloids, such as lactated Ringer's solution or Plasma-Lyte A) represent an increasingly used alternative to saline.[8] Several observational studies[6,9,10] and a before-and-after trial[5] suggested that the use of balanced crystalloids is associated with lower rates of acute kidney injury, renal-replacement therapy, and death. However, in two pilot trials,[11,12] no significant difference in any patient outcome was reported between those who received balanced crystalloids and those who received saline.

To determine the effect of isotonic crystalloid composition on clinical outcomes in critically ill adults, we conducted the Isotonic Solutions and Major Adverse Renal Events Trial (SMART), which compared the use of balanced crystalloids with the use of saline in patients in medical (SMART-MED) and nonmedical (SMART-SURG) intensive care units (ICUs). We hypothesized that the use of balanced crystalloids would result in a lower overall incidence of death, new renal-replacement therapy, and persistent renal dysfunction than saline.

Methods

Trial Design and Oversight

We conducted a pragmatic, unblinded, cluster-randomized, multiple-crossover trial in which the use of balanced crystalloids was compared with saline for intravenous fluid administration among critically ill adults admitted to five ICUs at Vanderbilt University Medical Center between June 1, 2015, and April 30, 2017. The trial was approved by the institutional review board at Vanderbilt University with a waiver of informed consent (see the Supplementary Appendix, available with the full text of this article at NEJM.org), was registered online before initiation, and was overseen by an independent data and safety monitoring board. The protocol, available at NEJM.org, and the statistical analysis plan were published before the conclusion of enrollment.[13] All authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Trial Sites and Patient Population

All adults (18 years of age or older) who were admitted to a participating ICU during the trial period were enrolled at the time of ICU admission (site characteristics are described in the Supplementary Appendix). Enrolled patients who were discharged from the hospital were eligible to participate again if they were readmitted to a participating ICU. We assessed the effect of repeat hospitalizations in individual patients in sensitivity analyses. Patients who were admitted to a non-ICU ward from the emergency department were enrolled in a separate trial (Saline against Lactated Ringer's or Plasma-Lyte in the Emergency Department [SALT-ED]) in which balanced crystalloids and saline were compared among adults who were not critically ill. The results of that trial are also reported in this issue of the *Journal*.[14]

Randomization

For each month of the trial, participating ICUs were assigned to use either balanced crystalloids or saline for any intravenous administration of isotonic crystalloid. ICUs were randomly assigned to use saline during even-numbered months and balanced crystalloids during odd-numbered months, or vice versa (Fig. S1 in the Supplementary Appendix). To allow coordination of crystalloid use between ICUs and the emergency department and operating rooms, the three ICUs that admit the majority of patients from the emergency department underwent randomization together, as did the two ICUs that admit the majority of patients from operating rooms.[13] Patients, clinicians, and investigators were aware of group assignments.

Treatments

Patients in the saline group received 0.9% sodium chloride when intravenous isotonic crystalloid was administered, whereas patients in the balanced-crystalloids group received either lactated Ringer's solution or Plasma-Lyte A, according to the preference of the treating clinician (Table S1 in the Supplementary Appendix). An electronic advisor

within the electronic order-entry system informed providers about the trial, asked about relative contraindications to the assigned crystalloid, and, if none were present, guided providers to order the assigned crystalloid. Relative contraindications to the use of balanced crystalloids included hyperkalemia and brain injury. The treating clinician determined the severity of hyperkalemia or brain injury at which saline rather than balanced crystalloids would be used. The unassigned crystalloid was also available from the pharmacy when clinicians believed it to be required for the safe treatment of any patient.

The trial was coordinated with the emergency department and operating rooms so that when feasible, patients being admitted to a participating ICU or receiving a surgical intervention during ICU admission would receive the crystalloid assigned to that ICU.[15] The need for access to an intravenous crystalloid at all times precluded the use of washout periods, and patients who remained in the ICU from the end of one calendar month to the start of another may have been exposed to both types of crystalloid. The effect of dual exposure was evaluated in prespecified sensitivity analyses.

DATA COLLECTION

We used data collected in routine care and electronically extracted from electronic health records.[12,16] These data included information on pre-enrollment renal function, demographic characteristics, diagnoses, predicted risk of in-hospital death, orders for intravenous fluids and blood products, plasma electrolyte and creatinine values, receipt of renal-replacement therapy, and vital status at hospital discharge. Trial personnel who were unaware of group assignment performed manual chart reviews to confirm receipt of renal-replacement therapy and identify indications for new renal-replacement therapy.

OUTCOMES

The primary outcome was the proportion of patients who met one or more criteria for a major adverse kidney event within 30 days[16-20] — the composite of death, new receipt of renal-replacement therapy, or persistent renal dysfunction (defined as a final inpatient creatinine value ≥200% of the baseline value) — all censored at hospital discharge or 30 days after enrollment, whichever came first. The National Institute of Diabetes and Digestive and Kidney Diseases work group on clinical trials in acute kidney injury recommends the use of a major adverse kidney event within 30 days as a patient-centered outcome for phase 3 trials.[16,18] We determined a value for baseline creatinine level using a previously described hierarchical approach in which creatinine values obtained during the year before hospitalization were given priority over in-hospital measurements obtained before ICU admission. The baseline creatinine level was estimated with a previously described three-variable formula when no pre-enrollment measurements were available (for details, see the Supplementary Appendix).[16,21] Patients who had received renal-replacement therapy before enrollment were ineligible to meet the criteria for new renal-replacement therapy or persistent renal dysfunction but could qualify for the primary outcome if they died in the hospital.

Secondary clinical outcomes included in-hospital death before ICU discharge or at 30 days or 60 days, as well as ICU-free days, ventilator-free days, vasopressor-free days, and days alive and free of renal-replacement therapy during the 28 days after enrollment.[13] Secondary renal outcomes included new receipt of renal-replacement therapy, persistent renal dysfunction, acute kidney injury of stage 2 or higher as defined in the Kidney Disease: Improving Global Outcomes criteria for creatinine level,[22] the highest creatinine level during the hospital stay, the change from baseline to the highest creatinine level, and the final creatinine level before hospital discharge.[13]

STATISTICAL ANALYSIS

Complete details regarding the sample-size justification have been reported previously.[13] Initially, we planned to enroll 8000 patients during 60 unit-months (12 months in five ICUs) to detect a 12% relative between-group difference[11,12] in the primary outcome of a major adverse kidney event within 30 days, assuming a 22.0% incidence of the outcome in the saline group on the basis of the findings in a previous report.[19] We subsequently obtained observational data for patients admitted to the ICUs involved in the trial in the year before the trial began. These data suggested that the incidence of the outcome in the saline group would be approximately 15.0%. To retain adequate power to detect the

targeted difference in relative risk, in collaboration with the data and safety monitoring board, the duration of the trial was increased to 82 unit-months. Enrolling approximately 14,000 patients during 82 unit-months would provide power of 90% at a type I error rate of 0.05 to detect a relative difference of 12% (an absolute difference of 1.9 percentage points) in the primary outcome between groups.[13] The data and safety monitoring board conducted two interim analyses; details are provided in the Supplementary Appendix.

Analyses were conducted at the level of each patient's hospitalization in an intention-to-treat fashion. Continuous variables are reported as means and standard deviations or as medians and interquartile ranges; categorical variables are reported as frequencies and proportions.

The primary analysis compared the incidence of the primary outcome in the balanced-crystalloids and saline groups with a generalized, linear, mixed-effects model that included fixed effects (group assignment, age, sex, race, source of admission, mechanical-ventilation status, vasopressor receipt, diagnosis of sepsis, and diagnosis of traumatic brain injury) and random effects (ICU to which the patient was admitted) (for details, see the Supplementary Appendix).[23,24] Both conditional (ICU-level) and marginal (population-level) effects are reported.

Prespecified secondary analyses involved a similar approach. First, we compared secondary outcomes between trial groups. Second, we performed subgroup analyses according to type of ICU, source of admission, receipt of mechanical ventilation, receipt of vasopressors, diagnosis of sepsis or traumatic brain injury (for details, see the Supplementary Appendix), baseline renal function, predicted in-hospital mortality, and total volume of isotonic crystalloid administered through day 30. Third, we conducted sensitivity analyses using alternative approaches to addressing the issue of missing data on baseline creatinine level (for details, see the Supplementary Appendix). Fourth, we performed sensitivity analyses according to the volume of crystalloid administered, accounting for crossover and limiting the analyses to each patient's first ICU admission.[13] Other between-group comparisons were made with the Mann–Whitney rank-sum test for continuous variables and the chi-square test for categorical variables.

A two-sided P value of less than 0.048 indicated statistical significance for the primary outcome after accounting for interim analyses. All other analyses were considered to be hypothesis-generating.[13] With 14 secondary outcomes, the likelihood of observing a P value of less than 0.05 for at least one secondary outcome by chance alone was 51.2%. All analyses were performed with the statistical software R, version 3.3.0, with a prespecified analysis code published before the conclusion of enrollment.[13]

RESULTS

BASELINE CHARACTERISTICS

In all, 15,802 patients from five ICUs were enrolled in the trial (Fig. S2 in the Supplementary Appendix). The median age was 58 years, and 57.6% of patients were men. More than one third of patients were receiving mechanical ventilation and one quarter were receiving vasopressors at enrollment. There were no significant differences in baseline characteristics between the patients assigned to receive balanced crystalloids (7942 patients) and those assigned to receive saline (7860 patients) (Table 1, and Tables S2 and S3 in the Supplementary Appendix).

FLUID THERAPY AND ELECTROLYTES

Because the fluid therapy provided in the emergency department and operating room was coordinated with that provided in the ICU to which patients were being admitted, the majority of pre-ICU fluid that patients received was consistent with trial-group assignment (Table S4 in the Supplementary Appendix). The median volume of balanced crystalloids administered to patients in the balanced-crystalloids group between ICU admission and hospital discharge or 30 days (whichever occurred first) was 1000 ml (interquartile range, 0 to 3210), and the median volume of 0.9% sodium chloride administered to patients in the saline group was 1020 ml (interquartile range, 0 to 3500) (Fig. 1, and Tables S5 and S6 in the Supplementary Appendix). Only 426 patients (5.4%) in the balanced-crystalloids group and 343 patients (4.4%) in the saline group received any volume of unassigned crystalloid as a result of remaining in the ICU from one calendar month to the next (Table S5 in the Supplementary Appendix). There was no significant between-group difference in the median

Table 1. Participant Characteristics at Baseline.*

Characteristic	Balanced Crystalloids (N=7942)	Saline (N=7860)
Age — yr		
Median	58	58
Interquartile range	44–69	44–69
Male sex — no. (%)	4540 (57.2)	4557 (58.0)
White race — no. (%)†	6384 (80.4)	6322 (80.4)
Weight — kg‡		
Median	80	79
Interquartile range	69–96	68–95
Coexisting renal conditions — no. (%)		
Chronic kidney disease of stage 3 or higher§	1388 (17.5)	1360 (17.3)
Previous receipt of renal-replacement therapy — no. (%)	384 (4.8)	402 (5.1)
Source of admission to ICU — no. (%)		
Emergency department	3975 (50.1)	3997 (50.9)
Operating room	1732 (21.8)	1649 (21.0)
Transfer from another hospital	1038 (13.1)	1018 (13.0)
Hospital ward	788 (9.9)	780 (9.9)
Outpatient	363 (4.6)	359 (4.6)
Another ICU within hospital	46 (0.6)	57 (0.7)
Diagnosis on ICU admission — no. (%)		
Sepsis or septic shock	1167 (14.7)	1169 (14.9)
Traumatic brain injury	698 (8.8)	665 (8.5)
Mechanical ventilation — no. (%)	2723 (34.3)	2731 (34.7)
Vasopressors — no. (%)	2094 (26.4)	2058 (26.2)
Mean predicted risk of in-hospital death — % (95% CI)¶	9.4 (9.0–9.9)	9.6 (9.2–10.0)
Baseline creatinine level — mg/dl‖		
Median	0.89	0.89
Interquartile range	0.74–1.10	0.74–1.10
Acute kidney injury of stage 2 or higher — no. (%)**	681 (8.6)	643 (8.2)

* There were no significant differences in baseline characteristics between the two study groups (P values range from 0.12 to 0.94). To convert the values for creatinine to micromoles per liter, multiply by 88.4. ICU denotes intensive care unit.

† Race was reported by patients or their surrogates and recorded in the electronic health record as a part of routine clinical care.

‡ Information on weight at enrollment was missing for 698 patients.

§ Chronic kidney disease of stage 3 or higher is defined as a glomerular filtration rate less than 60 ml per minute per 1.73 m^2, as calculated with the equation developed by the Chronic Kidney Disease Epidemiology Collaboration[25] with the patient's baseline creatinine value.

¶ Predicted risk of in-hospital death is an estimated probability of death before hospital discharge generated through the Vizient database (formerly known as the University HealthSystem Consortium).[26] Information on the predicted risk of in-hospital death was missing for 126 patients.

‖ For the purposes of the trial, the baseline creatinine level was defined as the lowest plasma creatinine level measured in the 12 months preceding hospitalization, unless not available, in which case the lowest plasma creatinine level measured between hospitalization and admission to the ICU was used. An estimated creatinine level was used for patients for whom there was no level available from the 12 months before hospitalization to the time of admission to the ICU. Baseline creatinine levels were estimated for a total of 863 patients (10.9%) in the balanced-crystalloids group and 826 patients (10.5%) in the saline group (Table S3 in the Supplementary Appendix).

** Acute kidney injury of stage 2 or higher is defined according to the Kidney Disease: Improving Global Outcomes creatinine criteria[22] as a first plasma creatinine value after enrollment of at least 200% of the baseline value or both a value greater than 4.0 mg per deciliter (350 μmol per liter) and an increase of at least 0.3 mg per deciliter (27 μmol per liter) from the baseline value.

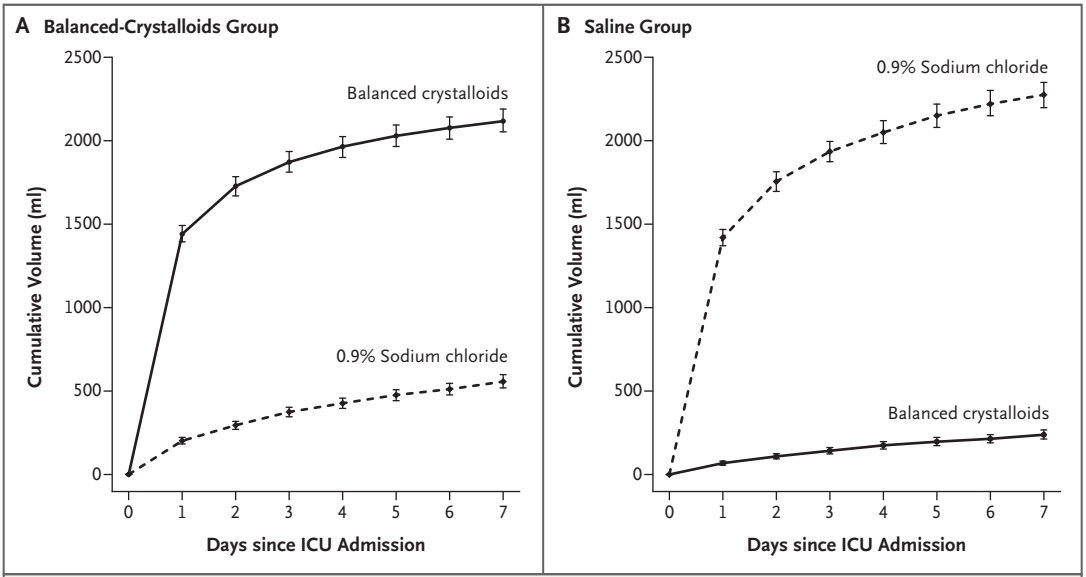

Figure 1. Volume of Intravenous Isotonic Crystalloid Administered According to Group.

The cumulative volume of intravenous balanced crystalloids (solid line) and 0.9% sodium chloride (dotted line) between admission to the intensive care unit (ICU) and hospital discharge is shown for patients in the balanced-crystalloids group (Panel A) and the saline group (Panel B). I bars indicate 95% confidence intervals.

volume of nonisotonic intravenous fluid, blood products, or medications administered (Table S7 in the Supplementary Appendix).

Fewer patients in the balanced-crystalloids group than in the saline group had a measured plasma chloride concentration greater than 110 mmol per liter (24.5% vs. 35.6%, P<0.001) or a plasma bicarbonate concentration less than 20 mmol per liter (35.2% vs. 42.1%, P<0.001) (Fig. 2, and Fig. S3 and Table S8 in the Supplementary Appendix). Differences between groups in chloride and bicarbonate concentration were greater for patients who received larger volumes of isotonic crystalloid (Figs. S4 and S5 in the Supplementary Appendix).

PRIMARY OUTCOME

A total of 1139 patients (14.3%) in the balanced-crystalloids group and 1211 patients (15.4%) in the saline group had a major adverse kidney event (marginal odds ratio, 0.91; 95% confidence interval [CI], 0.84 to 0.99; conditional odds ratio, 0.90; 95% CI, 0.82 to 0.99; P=0.04) (Table 2, and Table S9 and Fig. S6 in the Supplementary Appendix). The results were similar in six prespecified sensitivity analyses: one was restricted to patients who received 500 ml or more of isotonic crystalloid in the 72 hours after enrollment, a second excluded patients admitted in the week preceding a crossover in the fluid assigned to the ICU, a third excluded patients who transferred between ICUs or remained in the ICU through a crossover, a fourth included only the first ICU admission for each patient, a fifth addressed the issue of missing values for baseline creatinine levels, and a sixth used alternative modeling approaches (odds ratios between 0.87 and 0.93 for all sensitivity analyses; see Table S10 in the Supplementary Appendix). In prespecified subgroup analyses, the difference in the rate of the primary outcome between the balanced-crystalloids group and the saline group was greater among patients who received larger volumes of isotonic crystalloid and among patients with sepsis (Fig. 3, and Fig. S7 in the Supplementary Appendix). Among patients with sepsis, 30-day in-hospital mortality was 25.2% with balanced crystalloids and 29.4% with saline (adjusted odds ratio, 0.80; 95% CI, 0.67 to 0.97; P=0.02).

SECONDARY OUTCOMES

A total of 818 patients (10.3%) in the balanced-crystalloids group died before hospital discharge and within 30 days of ICU admission as compared with 875 patients (11.1%) in the saline group (P=0.06) (Table 2, and Figs. S8 and S9 in

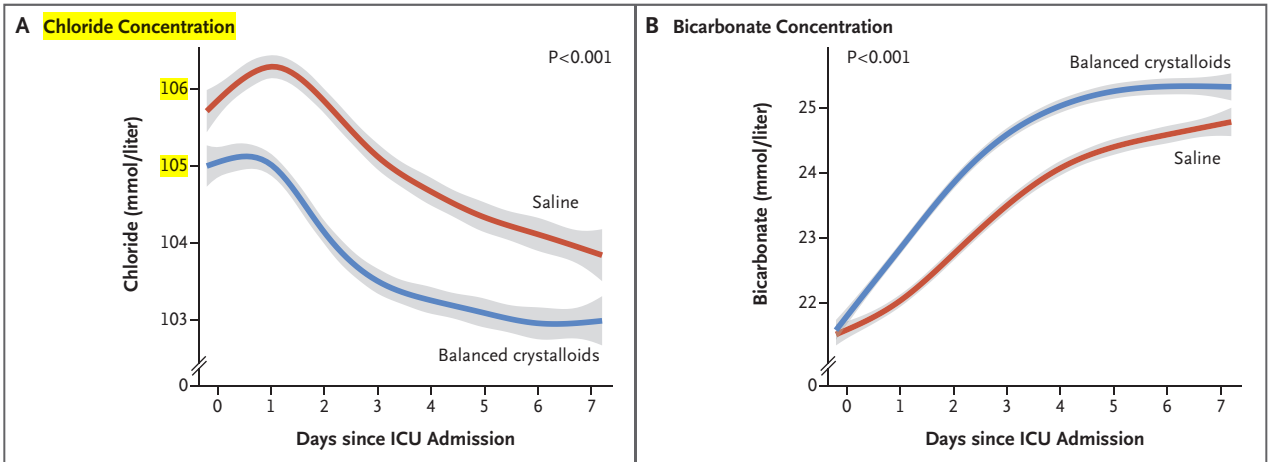

Figure 2. Plasma Chloride and Bicarbonate Concentration According to Group.

The mean and 95% confidence interval (denoted by gray shading) for the first measurement of plasma chloride concentration (Panel A) or bicarbonate concentration (Panel B) on the first 7 days since admission to the intensive care unit (ICU) are shown for patients in the balanced-crystalloids group and in the saline group with locally weighted scatterplot smoothing. Plasma chloride and bicarbonate concentrations were similar between groups at presentation (Table S3 in the Supplementary Appendix), but because fluid therapy in the emergency department and operating room was coordinated with the ICU to which patients were being admitted, plasma chloride concentration differed between the balanced-crystalloids and saline groups at the time of ICU admission.

the Supplementary Appendix). A total of 189 patients (2.5%) in the balanced-crystalloids group and 220 patients (2.9%) in the saline group received new renal-replacement therapy (P=0.08) (Table S11 in the Supplementary Appendix). The highest stage of acute kidney injury and the incidence of persistent renal dysfunction did not differ significantly between groups (Table 2, and Table S12 in the Supplementary Appendix).

DISCUSSION

Although both saline and balanced crystalloids have been administered to patients in clinical practice for decades,[3] few trials have addressed the effects of crystalloid composition on clinical outcomes.[1] In preclinical models, the high chloride content of saline has been reported to cause hyperchloremia,[27] acidosis,[27] inflammation,[28] renal vasoconstriction,[29] acute kidney injury,[30] hypotension,[31] and death.[32] Studies involving healthy volunteers suggest saline may decrease renal perfusion through chloride-mediated renal vasoconstriction.[33] Observational studies involving critically ill adults have shown higher rates of acute kidney injury,[34] renal-replacement therapy,[5,10] and death[6,7,9,35] with saline than with balanced crystalloids, although results have been inconsistent.[36] Although underpowered for clinical outcomes, two recent pilot trials involving critically ill adults showed an absolute difference of 1 percentage point in mortality in favor of balanced crystalloids.[11,12]

In the current trial, the use of balanced crystalloids rather than saline resulted in an absolute difference of 1.1 percentage points in favor of balanced crystalloids in the primary outcome. This finding is consistent with the results of the SALT-ED trial conducted concurrently in noncritically ill adults.[14] Although the effect size achieved in the current trial was modest in terms of percentages, if our data on the use of balanced crystalloids were applied to the care of the more than 5 million patients admitted to ICUs each year, the reduction in death, new renal-replacement therapy, or persistent renal dysfunction could be substantial.[37] Our results suggest that the use of balanced crystalloids rather than saline might prevent 1 patient among every 94 patients admitted to an ICU from the need for

Table 2. Clinical Outcomes.*

Outcome	Balanced Crystalloids (N=7942)	Saline (N=7860)	Adjusted Odds Ratio (95% CI)†	P Value†
Primary outcome				
Major adverse kidney event within 30 days — no. (%)‡	1139 (14.3)	1211 (15.4)	0.90 (0.82 to 0.99)	0.04
Components of primary outcome				
In-hospital death before 30 days — no. (%)	818 (10.3)	875 (11.1)	0.90 (0.80 to 1.01)	0.06
Receipt of new renal-replacement therapy — no./total no. (%)§	189/7558 (2.5)	220/7458 (2.9)	0.84 (0.68 to 1.02)	0.08
Among survivors	106/6787 (1.6)	117/6657 (1.8)		
Final creatinine level ≥200% of baseline — no./total no. (%)§	487/7558 (6.4)	494/7458 (6.6)	0.96 (0.84 to 1.11)	0.60
Among survivors	259/6787 (3.8)	273/6657 (4.1)		
Among survivors without new renal-replacement therapy	215/6681 (3.2)	219/6540 (3.3)		
Secondary outcomes				
In-hospital death — no. (%)				
Before ICU discharge	528 (6.6)	572 (7.3)	0.89 (0.78 to 1.02)	0.08
Before 60 days	928 (11.7)	975 (12.4)	0.92 (0.83 to 1.02)	0.13
ICU-free days¶				0.94
Median	25.3	25.3	1.00 (0.89 to 1.13)	
Interquartile range	22.1 to 26.6	22.2 to 26.6		
Mean	21.8±8.3	21.7±8.6		
Ventilator-free days¶			1.06 (0.97 to 1.16)	0.22
Median	28.0	28.0		
Interquartile range	26.0 to 28.0	26.0 to 28.0		
Mean	24.2±8.6	23.9±8.9		
Vasopressor-free days¶			1.05 (0.97 to 1.14)	0.26
Median	28.0	28.0		
Interquartile range	27.0 to 28.0	27.0 to 28.0		
Mean	24.7±8.5	24.4±8.8		
Renal-replacement therapy–free days¶			1.11 (1.02 to 1.20)	0.01
Median	28.0	28.0		
Interquartile range	28.0 to 28.0	28.0 to 28.0		
Mean	25.0±8.6	24.8±8.9		
Secondary renal outcomes§				
Stage 2 or higher AKI developing after enrollment — no./total no. (%)‖	807/7558 (10.7)	858/7458 (11.5)	0.91 (0.82 to 1.01)	0.09
Creatinine — mg/dl**				
Highest before discharge or day 30			1.01 (0.97 to 1.05)	0.58
Median	0.99	0.99		
Interquartile range	0.78 to 1.53	0.78 to 1.52		
Change from baseline to highest value			0.98 (0.94 to 1.02)	0.35
Median	0.04	0.04		
Interquartile range	−0.08 to 0.31	−0.08 to 0.32		

Table 2. (Continued.)

Outcome	Balanced Crystalloids (N=7942)	Saline (N=7860)	Adjusted Odds Ratio (95% CI)†	P Value†
Final value before discharge or 30 days			1.02 (0.97 to 1.06)	0.51
Median	0.83	0.83		
Interquartile range	0.70 to 1.11	0.70 to 1.11		

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. ICU denotes intensive care unit.

† Categorical outcomes were compared with a generalized, linear, mixed-effects model, with adjustment for the ICU to which the patient was admitted as a random effect and prespecified covariates as fixed effects.[13] Continuous outcomes were compared between groups with a proportional-odds model, with adjustment for the same variables.

‡ A major adverse kidney event within 30 days is the composite of death, receipt of new renal-replacement therapy, or final creatinine level that was at least 200% of the baseline level, with all events censored at hospital discharge or at 30 days after admission to the ICU, whichever occurred first. The effect of study group on major adverse kidney events within 30 days is the conditional effect. The marginal effect yielded an odds ratio of 0.91 and a 95% confidence interval of 0.84 to 0.99.

§ Data on receipt of new renal-replacement therapy, final creatinine level that was at least 200% of the baseline level, and secondary renal outcomes are provided for the 15,016 patients not known to have received renal-replacement therapy before ICU admission.

¶ ICU-free, ventilator-free, vasopressor-free, and renal-replacement-therapy–free days refer to the number of days on which a patient was alive and free from the specified therapy in the first 28 days after enrollment. Odds ratios of higher than 1.0 indicate a better outcome (i.e., more days alive and free from the specified therapy) with balanced crystalloids than with saline.

‖ The development of acute kidney injury (AKI) of stage 2 or higher after enrollment was defined in accordance with the Kidney Disease: Improving Global Outcomes plasma creatinine criteria[22] as any creatinine level between enrollment and discharge or 30 days that increased by at least 0.3 mg per deciliter (27 μmol per liter) from a preceding post-enrollment value and was at least 200% of the baseline value, at least 200% of a preceding post-enrollment value, or at least 4.0 mg per deciliter (350 μmol per liter) or as new receipt of renal-replacement therapy.

** Among patients who had not received previous renal-replacement therapy, the plasma creatinine level was measured a mean of 8.0 times between enrollment and the first of discharge or 30 days in each group; the plasma creatinine level was not measured between enrollment and the first of discharge or 30 days for 418 of 7558 patients (5.5%) in the balanced-crystalloids group and 443 of 7458 patients (5.9%) in the saline group.

new renal-replacement therapy, from persistent renal dysfunction, or from death. Moreover, the difference in outcomes between balanced crystalloids and saline appeared to be greater for patients with sepsis and patients who received larger volumes of isotonic crystalloid.

The appropriate composition of a fluid may depend on the indication for its use and the condition of the individual patient. Concern that the relative hypotonicity of balanced crystalloids could increase intracranial pressure in patients with brain injury led us to systematically present clinicians with the option of administering 0.9% sodium chloride to patients with brain injury, regardless of trial group. Thus, our results cannot be used to provide guidance as to whether balanced crystalloids should be used in patients with traumatic brain injury.

Our trial has several strengths. The large sample size provided statistical power to detect small differences in patient outcomes. As was the case in each of the previous trials that compared balanced crystalloids with saline in critically ill adults,[5,11,12] group assignment in our trial occurred at the level of the ICU. This trial design allowed delivery of the assigned crystalloid early in each patient's critical illness. Enrolling all adults admitted to participating ICUs and allowing clinical providers to deliver the assigned crystalloid during clinical care minimized selection bias and improved generalizability.

The trial also has several limitations. Conduct at a single academic center limits generalizability. Treating clinicians were aware of the composition of the assigned crystalloid and of the group-assignment sequence of their ICU. The outcomes of death and creatinine level are objective, but a clinician's decision to initiate renal-replacement therapy may be susceptible to treatment bias. Censoring data collection at hospital discharge may underestimate the true incidence of death at 30 days and may overestimate the true incidence of persistent renal dysfunction at 30 days.[16] On the basis of the hypothesized mechanism of chloride-induced organ injury or acidosis,[29,33] we evaluated lactated Ringer's solution and Plasma-Lyte A together, and this trial does not inform the choice between the two.

Subgroup	Balanced Crystalloids	Saline	Odds Ratio (95% CI)	P Value	P Value for Interaction
	no. of events/total no. (%)				
Unit					0.27
Medical	615/2735 (22.5)	659/2646 (24.9)	0.87 (0.77–0.99)	0.04	
Cardiac	202/1470 (13.7)	190/1501 (12.7)	1.10 (0.89–1.36)	0.38	
Neurologic	116/1440 (8.1)	141/1377 (10.2)	0.77 (0.59–0.99)	0.04	
Trauma	131/1640 (8.0)	142/1688 (8.4)	0.95 (0.74–1.21)	0.66	
Surgical	75/657 (11.4)	79/648 (12.2)	0.93 (0.66–1.30)	0.66	
Sepsis					0.06
No	744/6775 (11.0)	756/6691 (11.3)	0.96 (0.86–1.07)	0.47	
Yes	395/1167 (33.8)	455/1169 (38.9)	0.80 (0.67–0.94)	0.01	
Traumatic brain injury					0.24
No	1034/7244 (14.3)	1118/7195 (15.5)	0.89 (0.81–0.98)	0.01	
Yes	105/698 (15.0)	93/665 (14.0)	1.09 (0.81–1.47)	0.58	
Categories of kidney function					0.19
Normal	476/5596 (8.5)	514/5561 (9.2)	0.91 (0.80–1.04)	0.16	
Acute kidney injury	315/574 (54.9)	316/537 (58.8)	0.85 (0.67–1.08)	0.18	
Chronic kidney disease	301/1388 (21.7)	307/1360 (22.6)	0.95 (0.79–1.13)	0.55	
Previous renal-replacement therapy	47/384 (12.2)	74/402 (18.4)	0.61 (0.41–0.91)	0.01	
Overall	1139/7942 (14.3)	1211/7860 (15.4)	0.91 (0.83–0.99)	0.04	

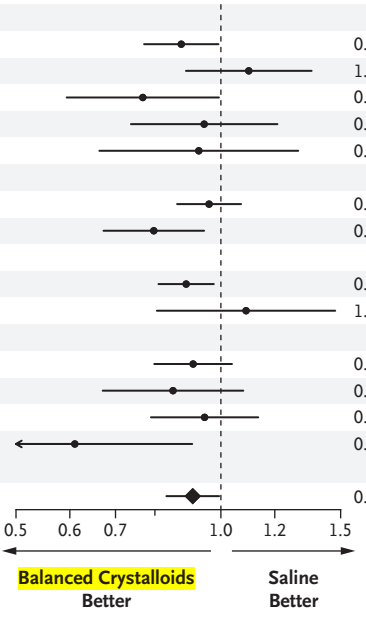

Figure 3. Subgroup Analysis of Rates for the Composite Outcome of Death, New Receipt of Renal-Replacement Therapy, or Persistent Renal Dysfunction.

The odds ratio and 95% confidence interval are shown overall and according to subgroup for the percentage of patients in the balanced-crystalloids group and the saline group who met the criteria for the composite outcome of death from any cause, new renal-replacement therapy, or persistent renal dysfunction. Normal kidney function refers to patients who had no acute kidney injury, chronic kidney disease, or renal-replacement therapy before enrollment. Acute kidney injury refers to patients without chronic kidney disease whose first creatinine level after enrollment was at least 200% of the baseline value or was both greater than 4.0 mg per deciliter (350 μmol per liter) and had increased at least 0.3 mg per deciliter (27 μmol per liter) from the value at baseline.[22] Chronic kidney disease refers to patients with a glomerular filtration rate less than 60 ml per minute per 1.73 m^2 as calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation with the value for the patient's baseline creatinine level.[25] Previous renal-replacement therapy refers to patients known to have received any form of renal-replacement therapy before enrollment.

In conclusion, in this trial involving critically ill adults, intravenous administration of balanced crystalloids rather than saline had a favorable effect on the composite outcome of death, new renal-replacement therapy, or persistent renal dysfunction.

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ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Noncritically Ill Adults

Wesley H. Self, M.D., M.P.H., Matthew W. Semler, M.D., Jonathan P. Wanderer, M.D., Li Wang, M.S., Daniel W. Byrne, M.S., Sean P. Collins, M.D., Corey M. Slovis, M.D., Christopher J. Lindsell, Ph.D., Jesse M. Ehrenfeld, M.D., M.P.H., Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D., and Todd W. Rice, M.D., for the SALT-ED Investigators*

ABSTRACT

BACKGROUND

Comparative clinical effects of balanced crystalloids and saline are uncertain, particularly in noncritically ill patients cared for outside an intensive care unit (ICU).

METHODS

We conducted a single-center, pragmatic, multiple-crossover trial comparing balanced crystalloids (lactated Ringer's solution or Plasma-Lyte A) with saline among adults who were treated with intravenous crystalloids in the emergency department and were subsequently hospitalized outside an ICU. The type of crystalloid that was administered in the emergency department was assigned to each patient on the basis of calendar month, with the entire emergency department crossing over between balanced crystalloids and saline monthly during the 16-month trial. The primary outcome was hospital-free days (days alive after discharge before day 28). Secondary outcomes included major adverse kidney events within 30 days — a composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction (defined as an elevation of the creatinine level to ≥200% of baseline) — all censored at hospital discharge or 30 days, whichever occurred first.

RESULTS

A total of 13,347 patients were enrolled, with a median crystalloid volume administered in the emergency department of 1079 ml and 88.3% of the patients exclusively receiving the assigned crystalloid. The number of hospital-free days did not differ between the balanced-crystalloids and saline groups (median, 25 days in each group; adjusted odds ratio with balanced crystalloids, 0.98; 95% confidence interval [CI], 0.92 to 1.04; P=0.41). Balanced crystalloids resulted in a lower incidence of major adverse kidney events within 30 days than saline (4.7% vs. 5.6%; adjusted odds ratio, 0.82; 95% CI, 0.70 to 0.95; P=0.01).

CONCLUSIONS

Among noncritically ill adults treated with intravenous fluids in the emergency department, there was no difference in hospital-free days between treatment with balanced crystalloids and treatment with saline. (Funded by the Vanderbilt Institute for Clinical and Translational Research and others; SALT-ED ClinicalTrials.gov number, NCT02614040.)

From the Departments of Emergency Medicine (W.H.S., S.P.C., C.M.S.), Anesthesiology (J.P.W., J.M.E., A.D.S.), Biomedical Informatics (J.P.W., J.M.E.), and Biostatistics (L.W., D.W.B., C.J.L.), the Division of Allergy, Pulmonary, and Critical Care Medicine, Department of Medicine (M.W.S., G.R.B., T.W.R.), and the Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt Center for Kidney Disease and Integrated Program for Acute Kidney Injury Research (E.D.S.), Vanderbilt University Medical Center, Nashville. Address reprint requests to Dr. Rice at the Department of Medicine, Vanderbilt University Medical Center, T-1218 MCN, 1161 21st Ave. S., Nashville, TN 37232, or at todd.rice@vanderbilt.edu.

*A complete list of the SALT-ED investigators is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Administration of intravenous isotonic crystalloids is one of the most common medical therapies, with routine use in emergency departments, hospital wards, intensive care units (ICUs), and operating rooms.[1] However, it is not known whether the composition of isotonic crystalloid fluid has an effect on patient outcomes.[1-3] In the United States, saline (0.9% sodium chloride; "normal saline") is the most commonly used isotonic crystalloid, with more than 200 million liters administered annually.[1] The chloride concentration of saline (154 mmol per liter) is higher than that of human plasma (94 to 111 mmol per liter). Infusion of saline generally causes hyperchloremic metabolic acidosis and may increase renal inflammation and impair renal perfusion.[4-8] Although the clinical significance of these physiological effects is incompletely understood, accumulating evidence suggests that the supraphysiologic chloride concentration of saline may contribute to kidney injury and impair a patient's ability to recover from severe illness.[9-15] The chloride concentration in physiologically balanced crystalloids, such as lactated Ringer's solution (109 mmol per liter) and Plasma-Lyte A (98 mmol per liter), are more similar to that of human plasma.[1,2]

Previous clinical studies that compared balanced crystalloids and saline have focused on critically ill patients in the ICU and operating room.[9-18] Although critically ill patients may be the most vulnerable to potential detrimental effects of saline, acutely ill patients without organ failure or other critical illness comprise a large patient population that is routinely treated with intravenous fluids.[1,19] Owing to the vast number of noncritically ill patients exposed to crystalloids, even small differences in the absolute risk of kidney injury or death between balanced crystalloids and saline may have large public health implications. In the present trial, we investigated the clinical effect of balanced crystalloids versus saline for routine intravenous fluid therapy in the emergency department among noncritically ill adults. We hypothesized that balanced crystalloids would result in earlier hospital discharge and a lower incidence of major adverse kidney events than saline.

Methods

Trial Design and Oversight

Our trial, the Saline against Lactated Ringer's or Plasma-Lyte in the Emergency Department (SALT-ED) trial, was a single-center, pragmatic, unblinded, multiple-crossover trial that compared balanced crystalloids and saline among consecutive noncritically ill adults treated with intravenous crystalloids in the emergency department before hospitalization outside the ICU. The rationale, design, and statistical analysis plan were prespecified and have been published.[20] The protocol is also available with the full text of this article at NEJM.org. The institutional review board at Vanderbilt University approved the trial with waiver of informed consent. The trial was monitored by an independent data and safety monitoring board.[20] The first and fourth authors vouch for the completeness and accuracy of the data and analyses.

Trial Population

The trial was conducted between January 1, 2016, and April 30, 2017, in the Vanderbilt University Medical Center Adult Emergency Department, a tertiary-care, academic, hospital-based emergency department in the United States with approximately 75,000 visits per year. The trial population consisted of adults (≥18 years old) who received at least 500 ml of intravenous isotonic crystalloids in the emergency department and were subsequently hospitalized outside an ICU. Patients who were admitted to an ICU from the emergency department were defined as critically ill and were enrolled in a separate trial that compared balanced crystalloids and saline among critically ill adults, the Isotonic Solutions and Major Adverse Renal Events Trial (SMART), reported in this issue of the *Journal*.[16] Patients who received less than 500 ml of crystalloids in the emergency department were excluded owing to the low dose of exposure to the intervention.[15] The unit of analysis was unique emergency department visit, with individual patients potentially contributing multiple visits. In a sensitivity analysis, we limited the trial population to the first emergency department visit among unique patients.

Treatment Assignments

The trial protocol guided the type of isotonic crystalloid that was administered in the emergency department. All other aspects of care were determined by treating clinicians independent of the trial protocol, including whether to treat with crystalloids and the volume of crystalloids administered. Consistent with the concept of a pragmatic clinical trial,[21] trial procedures were

embedded within routine care and executed by clinical personnel.

The methods of treatment assignment have been described previously.[20] In brief, the type of isotonic crystalloid was assigned according to calendar month, with all patients in the trial emergency department during the same month assigned to the same fluid, either balanced crystalloids or saline. During balanced-crystalloids months, clinicians had the option of choosing either lactated Ringer's solution or Plasma-Lyte A. Clinicians and patients were aware of the treatment assignments. The first trial month was assigned by means of computer-generated simple randomization. Treatment assignments then sequentially crossed over between balanced crystalloids and saline each month for a total of 16 months (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Selection of fluids after the patient's transfer from the emergency department to a hospital floor was not included as part of the trial intervention.

Electronic advisors within the electronic order-entry system informed providers about the trial, asked about relative contraindications to the assigned crystalloid, and guided them through crystalloid orders.[20] Relative contraindications to the use of balanced crystalloids included hyperkalemia and brain injury; the severity of hyperkalemia and brain injury at which saline was used instead of balanced crystalloids was determined by the treating provider. There were no relative contraindications listed for saline in the electronic advisor. Providers had the option of ordering off-protocol crystalloids if they believed an alternative was specifically indicated. Patients who received off-protocol fluids were included in the primary analysis according to intention-to-treat principles. In a secondary per-protocol analysis, the population was limited to patients who received all fluids in accordance with the protocol.

DATA COLLECTION

Data were extracted from the electronic medical record. We have previously validated these data-collection techniques for relevant data points.[15,22,23] Coexisting conditions at baseline were summarized with the Elixhauser Comorbidity Index score.[24]

OUTCOMES

The primary outcome was hospital-free days to day 28, a composite of in-hospital death and hospital length of stay defined as the number of days alive and out of the hospital between the index emergency department visit and 28 days later.[20,25] Patients who died during the index hospitalization and those hospitalized for more than 28 days were classified as having zero hospital-free days. For patients discharged alive before day 28, hospital-free days were calculated as 28 minus length of stay.

The trial included three key secondary outcomes: major adverse kidney events within 30 days, acute kidney injury of stage 2 or higher, and in-hospital death. Major adverse kidney events within 30 days was a composite of death, new renal-replacement therapy, or persistent renal dysfunction (final serum creatinine concentration, ≥200% of the baseline value) at the earliest of hospital discharge or 30 days after the index emergency department visit (Table S1 in the Supplementary Appendix).[26] Stage 2 or higher acute kidney injury was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) creatinine criteria as a maximum serum creatinine concentration at least 200% of the baseline value, an increase in the serum creatinine concentration to at least 4 mg per deciliter (354 μmol per liter) with an absolute increase of at least 0.5 mg per deciliter (44 μmol per liter), or initiation of new renal-replacement therapy before the earliest of hospital discharge or 30 days after the index emergency department visit.[27] In-hospital death was defined as death before hospital discharge, regardless of hospital length of stay.

Patients with end-stage renal disease who were receiving long-term renal-replacement therapy at presentation were not eligible to meet renal outcomes, including new renal-replacement therapy, persistent renal dysfunction, and acute kidney injury. However, patients with end-stage renal disease could meet the outcome of major adverse kidney events within 30 days through death. The baseline creatinine value was defined as the lowest recorded value within the electronic medical record at the trial institution in the year before presentation in the emergency department. Patients with no recorded creatinine values in the previous year had a baseline creatinine value calculated under the assumption of normal baseline renal function with the use of the following equation: [creatinine (in milligrams per deciliter) = 0.74 − 0.2 (if patient is female) + 0.08 (if patient is black) + 0.003 × age (in years)].[28] The serum creatinine concentration in the emergency department was defined as the first re-

corded value during the index emergency department visit. Creatinine values in the emergency department were considered to be baseline characteristics, whereas creatinine values after hospital admission were considered outcomes. Major adverse kidney events within 30 days and acute kidney injury were calculated on the basis of creatinine values after admission. Patients who presented to the emergency department with a creatinine value that met the criteria for acute kidney injury and who then had a drop in creatinine such that no value after hospital admission met these criteria did not have an outcome of acute kidney injury for the purposes of this trial. Additional, exploratory outcomes are described in Table S2 in the Supplementary Appendix.

STATISTICAL ANALYSIS

A trial duration of 16 months was selected to ensure numerous alternating periods of balanced crystalloids and saline, enrollment throughout the academic and calendar year, coordination with the concomitant trial (SMART),[16] and adequate sample size (power) to balance baseline characteristics and detect at least a 0.5-day difference in hospital-free days between groups. Sample size was dependent on the number of patients treated with isotonic crystalloids in the trial emergency department and hospitalized outside an ICU during the 16-month trial period. All the patients who met these criteria were enrolled. On the basis of historical data from the trial emergency department, we estimated that approximately 14,000 patients would be enrolled in 16 months, with the saline group having a mean (±SD) of 24±4 hospital-free days. Under these assumptions, 14,000 patients would provide more than 90% power to detect a difference of 0.5 hospital-free days between groups with a type I error rate of 0.05. One interim analysis was completed by the data and safety monitoring board at the midpoint of enrollment, which resulted in a recommendation to continue enrollment for the planned 16 months.[20]

An intention-to-treat analysis of eligible patients who were assigned to balanced crystalloids or saline was completed for the primary and secondary outcomes. Hospital-free days were analyzed with a multivariable proportional-odds model. Major adverse kidney events within 30 days, acute kidney injury, and in-hospital death were analyzed with multivariable logistic-regression models. Each model was adjusted for the following baseline characteristics: age, sex, race, admitting inpatient service, and days elapsed since the initiation of the trial.[20]

Heterogeneity of treatment effect was evaluated by adding an interaction term[29] to the models between trial-group assignment and each of the following prespecified baseline characteristics: serum creatinine, chloride, and bicarbonate concentrations in the emergency department; age; hospital admission service; and volume of crystalloid administered in the emergency department. A per-protocol secondary analysis was performed that included patients treated exclusively with the assigned crystalloid in the emergency department (100% adherence to trial treatment assignments).

A two-sided P value of less than 0.049 was considered to indicate statistical significance for the primary outcome after we accounted for one interim analysis with a Haybittle–Peto boundary of less than 0.001. With the use of the Bonferroni approach, a two-sided P value of less than 0.017 was considered to indicate statistical significance for the three key secondary outcomes: major adverse kidney events within 30 days, acute kidney injury, and in-hospital death. Analyses were conducted with R software, version 3.2.0 (R Foundation for Statistical Computing), and STATA software, version 14 (StataCorp).

RESULTS

PATIENTS

During the 16-month trial, 19,949 patients were treated with isotonic crystalloids in the emergency department and hospitalized; 3689 patients received less than 500 ml of crystalloids and were excluded, whereas 2913 patients were admitted from the emergency department to an ICU and enrolled in SMART[16] (Fig. S2 in the Supplementary Appendix). The final sample size was 13,347 patients, including 6708 (50.3%) assigned to balanced crystalloids and 6639 (49.7%) assigned to saline. Baseline creatinine values were calculated for 4666 patients (35.0%) who did not have an available measured value. Baseline characteristics were similar between the two groups, including demographic characteristics, burden of coexisting conditions, admitting service, and renal function (Table 1).

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Balanced Crystalloids (N=6708)	Saline (N=6639)
Median age (IQR) — yr	54 (37–67)	53 (37–67)
Female sex — no. (%)	3507 (52.3)	3379 (50.9)
Race — no. (%)†		
White	5159 (76.9)	5189 (78.2)
Black	1335 (19.9)	1251 (18.8)
Other	214 (3.2)	199 (3.0)
Median Elixhauser Comorbidity Index score (IQR)‡	7 (3–14)	7 (3–14)
Admission service — no. (%)		
Medicine services		
General medicine	4747 (70.8)	4687 (70.6)
Cardiology	303 (4.5)	321 (4.8)
Neurology	117 (1.7)	144 (2.2)
Surgery services		
General surgery	1278 (19.1)	1211 (18.2)
Trauma	263 (3.9)	276 (4.2)
Median baseline serum creatinine (IQR) — mg/dl	0.84 (0.71–0.95)	0.85 (0.71–0.94)
Source of baseline creatinine — no. (%)		
Measured value in medical record	4405 (65.7)	4276 (64.4)
Calculated value by equation	2303 (34.3)	2363 (35.6)
Initial kidney function in ED		
Serum creatinine		
Mean — mg/dl	1.32±1.42	1.31±1.36
Median (IQR) — mg/dl	0.93 (0.77–1.33)	0.93 (0.77–1.32)
≥1.5 mg/dl — no. (%)	1246 (18.6)	1240 (18.7)
End-stage renal disease with long-term renal-replacement therapy — no. (%)	126 (1.9)	109 (1.6)
Stage 2 or higher acute kidney injury — no./total no. (%)§	643/6582 (9.8)	631/6530 (9.7)
Initial serum electrolytes in ED		
Sodium — mmol/liter	137.2±4.2	137.4±4.3
Chloride — mmol/liter	102.8±5.4	103.1±5.6
Potassium — mmol/liter	4.1±0.7	4.1±0.7
Bicarbonate — mmol/liter	22.7±3.8	22.8±3.7
Blood urea nitrogen — mg/dl	20±16	20±16

* Plus–minus values are means ±SD. There were no significant differences in baseline characteristics between the two groups, except for initial serum sodium (P=0.006) and chloride (P=0.003). To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357. ED denotes emergency department, and IQR interquartile range.

† Race was reported by patients or their surrogates and recorded in the electronic health record as a part of routine clinical care.

‡ The Elixhauser Comorbidity Index score summarizes the burden of a patient's coexisting conditions. Scores range from −19 to 89, with higher scores indicating a profile of coexisting conditions that is more strongly associated with in-hospital death.[24]

§ Acute kidney injury was defined according to the Kidney Disease: Improving Global Outcomes creatinine criteria. Patients with end-stage renal disease who were receiving long-term renal-replacement therapy at the time of ED arrival were not eligible for the outcome of acute kidney injury.

Table 2. Crystalloids Received in the Emergency Department According to Assigned Treatment Group.*

Variable	Balanced Crystalloids (N=6708)	Saline (N=6639)
Total crystalloid volume		
Mean — ml	1608±1095	1597±1105
Median (IQR) — ml	1089 (1000–2000)	1071 (1000–2000)
≥2000 ml — no. (%)	2207 (32.9)	2150 (32.4)
Median volume of balanced crystalloids (IQR) — ml	1000 (1000–2000)	0
Median volume of saline (IQR) — ml	0	1000 (1000–2000)
Percentage of crystalloid volume consistent with assigned group — no. (%)		
100%: per-protocol population	5620 (83.8)	6160 (92.8)
51–99%	514 (7.7)	270 (4.1)
1–50%	254 (3.8)	131 (2.0)
0%	320 (4.8)	78 (1.2)

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding.

CRYSTALLOID TREATMENT

Patients received a median crystalloid volume of 1079 ml (interquartile range, 1000 to 2000). Most balanced crystalloids were administered as lactated Ringer's solution (95.3%), with a small percentage administered as Plasma-Lyte A (4.7%). Overall, 88.3% of the patients received only the assigned crystalloid in the emergency department with no use of off-protocol crystalloids. The volume of crystalloid that was administered and the adherence to crystalloid assignment were similar in the balanced-crystalloids and saline groups (Table 2, and Fig. S3 in the Supplementary Appendix).

SERUM ELECTROLYTE CONCENTRATIONS

After treatment with intravenous fluids in the emergency department, patients in the balanced-crystalloids group had lower chloride and higher bicarbonate concentrations than those in the saline group; these differences persisted for several days into the hospitalization (Fig. 1). Hyperchloremia (serum chloride concentration, >110 mmol per liter) and acidemia (serum bicarbonate concentration, <20 mmol per liter) were less common after treatment with balanced crystalloids than with saline (Table S3 in the Supplementary Appendix).

INTENTION-TO-TREAT ANALYSIS

There was no difference in the number of hospital-free days between patients in the balanced-crystalloids and saline groups (median, 25 days in each group; adjusted odds ratio with balanced crystalloids, 0.98; 95% confidence interval [CI], 0.92 to 1.04; P=0.41) (Table 3, and Fig. S4 in the Supplementary Appendix). Patients in the balanced-crystalloids group had a lower incidence of major adverse kidney events within 30 days than those in the saline group (4.7% vs. 5.6%; adjusted odds ratio, 0.82; 95% CI, 0.70 to 0.95; P=0.01). A lower count for each component of major adverse kidney events — death, renal-replacement therapy, and persistent renal dysfunction — in the balanced-crystalloids group contributed to the lower incidence of the composite outcome (Table 3, and Fig. S5 in the Supplementary Appendix). Stage 2 or higher acute kidney injury occurred in 8.0% of patients in the balanced-crystalloids group and 8.6% of patients in the saline group (adjusted odds ratio, 0.91; 95% CI, 0.80 to 1.03; P=0.14). Other clinical outcomes did not differ significantly between the two groups (Table S3 in the Supplementary Appendix).

HETEROGENEITY OF TREATMENT EFFECT

Hospital-free days were similar for patients in the balanced-crystalloids and saline groups across a

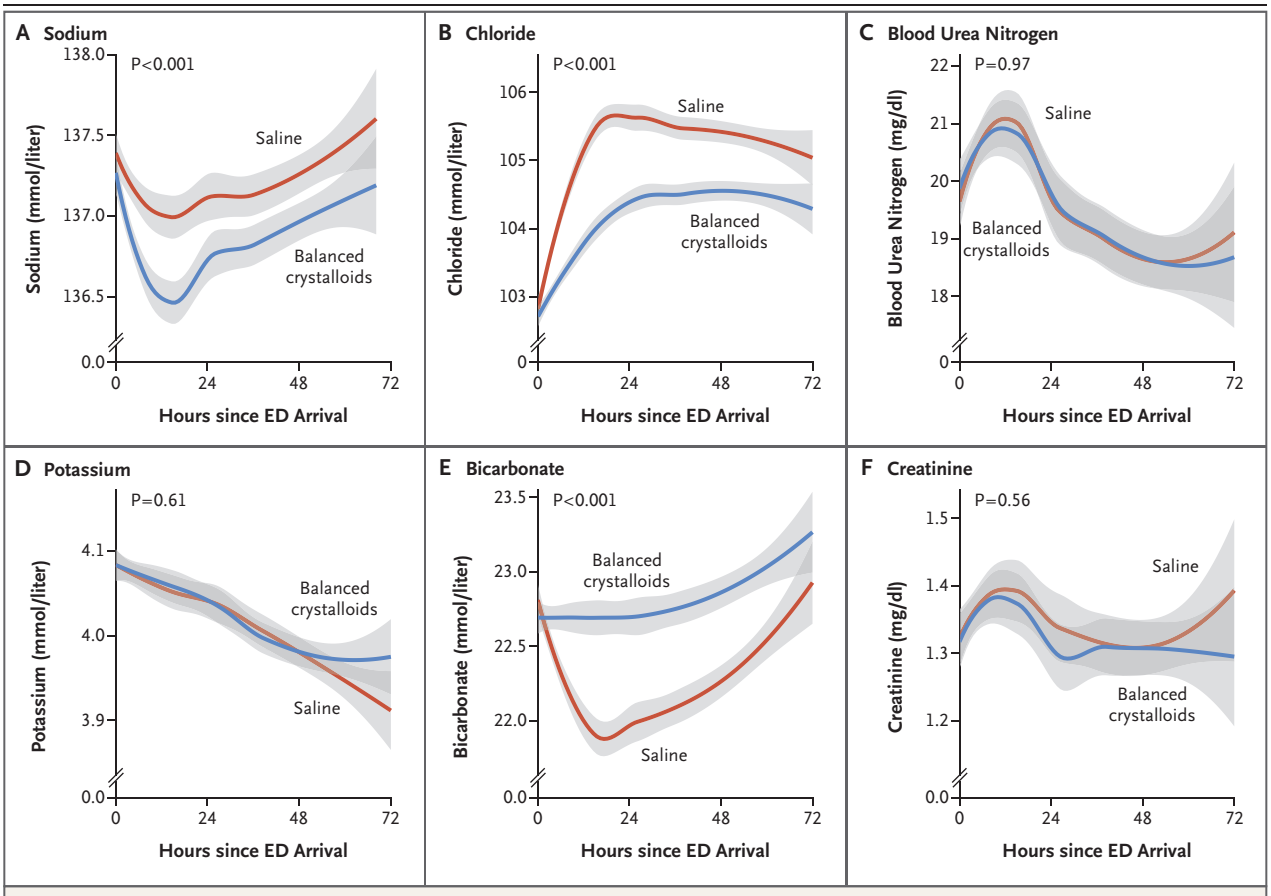

Figure 1. Serum Electrolyte Concentrations in the First 72 Hours after Arrival in the Emergency Department (ED).

Lines and bands represent means and 95% confidence intervals, respectively. Plots were generated with the use of locally weighted scatterplot smoothing. The P values in the figure represent the overall difference between groups, calculated with the use of proportional-odds models. Over time, the separation between groups increased for chloride (P<0.001 for interaction) and bicarbonate (P<0.001 for interaction); interaction terms for the other variables were not significant. To convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

broad range of baseline characteristics (Fig. 2). Patients who presented to the emergency department with renal dysfunction (serum creatinine concentration, ≥1.5 mg per deciliter [133 μmol per liter]) or hyperchloremia (serum chloride concentration, >110 mmol per liter) appeared to have the largest benefit from balanced crystalloids for avoiding major adverse kidney events within 30 days and acute kidney injury. Among patients who presented to the emergency department meeting KDIGO criteria for stage 2 or higher acute kidney injury (1274 patients), resolution of acute kidney injury during hospitalization was more common with balanced crystalloids, as shown by a lower incidence of major adverse kidney events within 30 days in the balanced-crystalloids group (28.0%) than in the saline group (37.6%) (P<0.001).

SENSITIVITY AND PER-PROTOCOL ANALYSES

Sensitivity analyses that were adjusted for period effect and that limited the trial population to patients without end-stage renal disease at presentation in the emergency department (13,112 patients), to patients with a measured baseline serum creatinine value (8681 patients), and to the first emergency department visit among unique patients in the trial (10,573 patients) all produced results similar to those of the primary analysis (Table S4 in the Supplementary Appendix).

Table 3. Clinical Outcomes According to Assigned Treatment Group in the Intention-to-Treat Analysis.

Outcome	Balanced Crystalloids (N=6708)	Saline (N=6639)	Adjusted Odds Ratio (95% CI)*	Adjusted P Value
Median hospital-free days to day 28 (IQR)	25 (22–26)	25 (22–26)	0.98 (0.92–1.04)	0.41
Major adverse kidney event within 30 days — no. (%)	315 (4.7)	370 (5.6)	0.82 (0.70–0.95)	0.01
Death — no. (%)	94 (1.4)	102 (1.5)	0.89	
New renal-replacement therapy — no./total no. (%)†	18/6582 (0.3)	31/6530 (0.5)	0.56	
Final serum creatinine ≥200% of baseline — no./total no. (%)†	253/6582 (3.8)	293/6530 (4.5)	0.84	
Stage 2 or higher acute kidney injury — no./total no. (%)†	528/6582 (8.0)	560/6530 (8.6)	0.91 (0.80–1.03)	0.14
In-hospital death — no. (%)	95 (1.4)	105 (1.6)	0.88 (0.66–1.16)	0.36

* Multivariable models were adjusted for age, sex, race, admitting service, and time (days since trial initiation).
† Patients with end-stage renal disease who were receiving long-term renal-replacement therapy at the time of emergency department arrival (126 in the balanced-crystalloids group and 109 in the saline group) were not eligible for the following outcomes: new renal-replacement therapy within 30 days, final serum creatinine concentration within 30 days at least 200% of the baseline value, and stage 2 or higher acute kidney injury.

The per-protocol analysis (11,780 patients) also produced similar results (Tables S5 and S6 in the Supplementary Appendix).

DISCUSSION

In this pragmatic trial of noncritically ill adults treated with intravenous fluid in the emergency department, treatment with balanced crystalloids did not result in a shorter time to hospital discharge (hospital-free days) than treatment with saline but did result in a lower incidence of the composite of death, new renal-replacement therapy, and persistent renal dysfunction (major adverse kidney events within 30 days), which was a secondary outcome. The lower incidence of major adverse kidney events within 30 days in the balanced-crystalloids group is consistent with the results of SMART, which was conducted concurrently in critically ill adults.[16]

Patients in the present trial had lower risks of renal outcomes and death overall than critically ill adults requiring ICU admission.[10,15,16,30] Despite these lower risks, there was an absolute difference of 0.9 percentage points in the risk of major adverse kidney events within 30 days in favor of the balanced-crystalloids group, corresponding to a number needed to treat of 111. Although this risk difference is modest for each patient, implications on a population level may be substantial owing to the millions of patients who receive isotonic crystalloids annually.[1,19] Operationally, lactated Ringer's solution and saline are similar in terms of cost, availability, and procedures for administration.[2,31]

A strength of our trial was high adherence to the assigned crystalloid group. Use of an unblinded, pragmatic design in a learning health care system[32] facilitated incorporation of the trial into routine practice, allowing the assigned crystalloid to be systematically used for early fluid resuscitation immediately after arrival in the emergency department.

Limitations of the trial include its single-center setting, unblinded design, and outcome ascertainment that was limited to the index hospitalization. Owing to the pragmatic design that used data collection from the electronic medical record, more detailed information about patient characteristics was not available. In addition, crystalloids used for intravenous fluid therapy in the emergency department were included in the trial intervention, but fluids administered after hospital admission and those used as medication carriers were not controlled. Lactated Ringer's solution represented more than

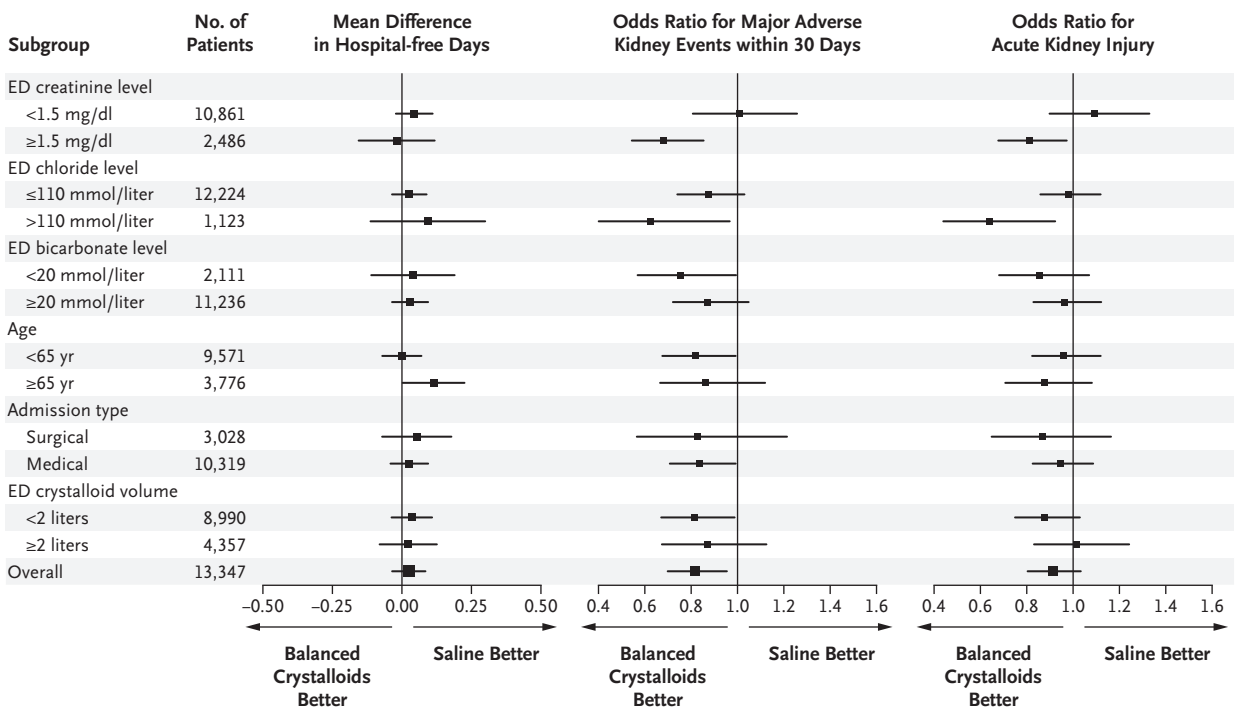

Figure 2. Heterogeneity of Treatment Effect.

Shown are forest plots for hospital-free days to day 28, major adverse kidney events within 30 days, and acute kidney injury of stage 2 or higher according to Kidney Disease: Improving Global Outcomes creatinine criteria. The outcome of major adverse kidney events within 30 days was a composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction (defined as an elevation of the creatinine level to ≥200% of baseline) — all censored at hospital discharge or 30 days, whichever occurred first. Patients with end-stage renal disease who were receiving long-term renal-replacement therapy at the time of arrival in the emergency department (235 patients) were not eligible for the outcome of acute kidney injury; hence, the total sample size for the analysis of acute kidney injury was 13,112.

95% of the balanced crystalloids used in the trial; additional study is required to compare Plasma-Lyte A with both saline and lactated Ringer's solution. Last, this trial evaluated balanced crystalloids versus saline as the routine, first-line isotonic fluid in a broad patient population; fluid selection that is tailored to specific patient characteristics is an alternative approach that was not evaluated in this trial.

In conclusion, in this pragmatic clinical trial involving noncritically ill adults treated with intravenous fluids in the emergency department, the number of hospital-free days, the primary outcome of the trial, did not differ between patients assigned to balanced crystalloids and those assigned to saline.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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