Balanced Crystalloids versus Saline in Noncritically Ill Adults

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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. (Backed by the Vanderbilt Institute for Clinical and Translational Research and others; SALT-ED ClinicaTrials.gov number, NCT02614040.)
ADMINISTRATION OF INTRAVENOUS ISO-
tonic crystalloids is one of the most com-
mon medical therapies, with routine use
in emergency departments, hospital wards, inten-
sive care units (ICUs), and operating rooms.1
However, it is not known whether the composi-
tion of isotonic crystalloid fluid has an effect on
patient outcomes.23 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 an-
nually.1 The chloride concentration of saline
(154 mmol per liter) is higher than that of hu-
man plasma (94 to 111 mmol per liter). Infusion
of saline generally causes hyperchloremic meta-
bolic acidosis and may increase renal inflamma-
tion and impair renal perfusion.4-8 Although
the clinical significance of these physiological
effects is incompletely understood, accumulating
evidence suggests that the supraphysiologic chlo-
ride concentration of saline may contribute to
kidney injury and impair a patient’s ability to re-
cover from severe illness.9-21 The chloride concen-
tration 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 bal-
anced crystalloids and saline have focused on
critically ill patients in the ICU and operating
room.5-28 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 intrave-
nous fluids.1,19 Owing to the vast number of non-
critically 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 emergen-
cy department among noncritically ill adults. We
hypothesized that balanced crystalloids would re-
result in earlier hospital discharge and a lower inci-
dence 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 consecu-
tive noncritically ill adults treated with intrave-
nous crystalloids in the emergency department
before hospitalization outside the ICU. The ra-
tionale, design, and statistical analysis plan were
prespecified and have been published.20 The pro-
tocol 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 approxi-
mately 75,000 visits per year. The trial population
consisted of adults (≥18 years old) who received
at least 500 ml of intravenous isotonic crystal-
loids in the emergency department and were
subsequently hospitalized outside an ICU. Patients
who were admitted to an ICU from the emergen-
cy department were defined as critically ill
and were enrolled in a separate trial that com-
pared balanced crystalloids and saline among criti-
cally ill adults, the Isotonic Solutions and Major
Adverse Renal Events Trial (SMART), reported in
this issue of the Journal.26 Patients who received
less than 500 ml of crystalloids in the emergen-
cy 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 contrib-
uting 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 emer-
gency 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 ad-
ministered. Consistent with the concept of a
pragmatic clinical trial,21 trial procedures were

A Quick Take

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embedded within routine care and executed by clinical personnel.

The methods of treatment assignment have been described previously. 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 crystalsloids 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 crystalloids orders. 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. Coexisting conditions at baseline were summarized with the Elixhauser Comorbidity Index score.

**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. 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). 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. 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)]. 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), 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.

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.

Heterogeneity of treatment effect was evaluated by adding an interaction term 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 (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.*

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

* 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.
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

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

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

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding.
Balanced Crystalloids in Noncritically Ill Adults

A 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).
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.20,15,16,30 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 system32 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

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

* 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.
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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