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Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults

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ABSTRACT

BACKGROUND

Whether the use of balanced multielectrolyte solution (BMES) in preference to 0.9% sodium chloride solution (saline) in critically ill patients reduces the risk of acute kidney injury or death is uncertain.

METHODS

In a double-blind, randomized, controlled trial, we assigned critically ill patients to receive BMES (Plasma-Lyte 148) or saline as fluid therapy in the intensive care unit (ICU) for 90 days. The primary outcome was death from any cause within 90 days after randomization. Secondary outcomes were receipt of new renal-replacement therapy and the maximum increase in the creatinine level during ICU stay.

RESULTS

A total of 5037 patients were recruited from 53 ICUs in Australia and New Zealand — 2515 patients were assigned to the BMES group and 2522 to the saline group. Death within 90 days after randomization occurred in 530 of 2433 patients (21.8%) in the BMES group and in 530 of 2413 patients (22.0%) in the saline group, for a difference of −0.15 percentage points (95% confidence interval [CI], −3.60 to 3.30; P=0.90). New renal-replacement therapy was initiated in 306 of 2403 patients (12.7%) in the BMES group and in 310 of 2394 patients (12.9%) in the saline group, for a difference of −0.20 percentage points (95% CI, −2.96 to 2.56). The mean (±SD) maximum increase in serum creatinine level was 0.41±1.06 mg per deciliter (36.6±94.0 μmol per liter) in the BMES group and 0.41±1.02 mg per deciliter (36.1±90.0 μmol per liter) in the saline group, for a difference of 0.01 mg per deciliter (95% CI, −0.05 to 0.06) (0.5 μmol per liter [95% CI, −4.7 to 5.7]). The number of adverse and serious adverse events did not differ meaningfully between the groups.

CONCLUSIONS

We found no evidence that the risk of death or acute kidney injury among critically ill adults in the ICU was lower with the use of BMES than with saline. (Funded by the National Health and Medical Research Council of Australia and the Health Research Council of New Zealand; PLUS ClinicalTrials.gov number, NCT02721654.)

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*The Plasma-Lyte 148 versus Saline (PLUS) Study investigators are listed in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

The choice of intravenous fluids administered in patients treated in an intensive care unit (ICU) is known to influence patient outcomes. For example, the use of 4% albumin has been associated with increased mortality among patients with traumatic brain injury,[1,2] and the use of hydroxyethyl starch has been associated with an increased risk of kidney injury and death.[3,4] Globally, 0.9% sodium chloride solution (saline) has been the fluid most commonly administered in patients in ICUs.[5] More recently, concerns that saline may increase the risk of acute kidney injury[6-8] — and in some cohorts the risk of death[9,10] — have resulted in increased use of balanced salt solutions (i.e., crystalloid solutions with a chloride concentration closer to that in human plasma).[11,12] However, whether the use of balanced solutions improves outcomes in patients in ICUs remains uncertain.[13,14] An open-label, cluster-crossover trial conducted at the ICUs of a single medical center in the United States compared balanced salt solutions with saline and showed better outcomes with balanced solutions[8]; however, a smaller double-blind, cluster-randomized, double-crossover trial conducted at the ICUs of four hospitals in New Zealand showed no benefit.[15]

To address this clinical uncertainty, we conducted the Plasma-Lyte 148 versus Saline (PLUS) Study in Australia and New Zealand. We tested the hypothesis that 90-day mortality among critically ill adults would be lower with the use of fluid resuscitation and therapy with Plasma-Lyte 148, a balanced multielectrolyte solution (BMES), than with saline.

Methods

Trial Oversight

The PLUS Study was an investigator-initiated, double-blind, parallel-group, randomized, controlled trial and was designed by the trial-management committee, the members of which are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org. The trial was sponsored by the George Institute for Global Health, endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group, and funded by the National Health and Medical Research Council (Australia) and the Health Research Council of New Zealand. Baxter Healthcare (Australia) supplied and distributed the trial fluids. Neither the funding agencies nor Baxter Healthcare had input into the design or conduct of the trial, the analysis or interpretation of the data, or the writing of the manuscript. Data were collected by research coordinators employed by the participating hospitals. The authors wrote the manuscript and made the decision to submit it for publication.

The trial protocol and subsequent amendments,[16,17] available at NEJM.org, were approved by the human research ethics committee for each participating hospital. The statistical analysis plan, available with the protocol, has been published previously.[18] Statistical analyses were conducted at the George Institute for Global Health. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Trial Patients

Patients 18 years of age or older who had been admitted to one of 53 participating ICUs during the period from September 2017 through December 2020 were assessed for eligibility. Patients for whom fluid resuscitation was judged by the treating clinician to be necessary (with the use of BMES or saline considered to be equally appropriate) were eligible if they were expected to be in the ICU on 3 consecutive days. Patients were excluded if they had specific fluid requirements, had received disqualifying fluid resuscitation (initially considered to be any volume and later amended to be >500 ml of fluid prescribed and administered in the ICU), were at imminent risk for death or had a preexisting life expectancy of less than 90 days, or had traumatic brain injury or were at risk for cerebral edema (see the Supplementary Appendix). Written or oral informed consent or consent to continue trial interventions and allow personal data to be analyzed was obtained from each patient or a legally authorized representative.

Randomization and Interventions

Randomization was performed with the use of permuted blocks of varying size, stratified according to ICU, and was conducted through a secure website. The trial fluids were supplied in identical 1000-ml bags, and the trial-group assignments were concealed from the patients, the

patients' legally authorized representatives, researchers, and treating clinicians before and after randomization.

For up to 90 days after randomization, patients received the assigned trial fluid for all fluid resuscitation and compatible crystalloid therapy in the ICU. Other crystalloid fluids, preferably 5% glucose solution, were used to dilute drugs for which either trial fluid was incompatible. The treating clinicians decided the amount and rate of fluid administration. Once the patient was outside the ICU, the type of fluid administered was not dictated by the trial protocol. All other treatments were administered at the discretion of the treating clinicians.

DATA AND TRIAL MANAGEMENT

Patient data collected at baseline included demographic characteristics, the Acute Physiology and Chronic Health Evaluation (APACHE) II score (range, 0 to 71, with higher scores indicating an increased risk of death),[19] and information necessary for the diagnosis of sepsis.[20,21] Data that were recorded daily during the first 7 days after randomization included hemodynamic variables, volumes of fluids and blood products administered, urine output, organ support, laboratory data, and data to derive the Sequential Organ Failure Assessment (SOFA) score (range, 0 to 4 in each of six domains, with higher scores indicating increasing organ dysfunction). Data that were recorded daily from day 8 through day 90 included ventilation and renal-replacement therapy status, cardiovascular SOFA score, serum creatinine level, and volume of trial fluid administered.

OUTCOME MEASURES

The primary outcome was death from any cause within 90 days after randomization. Secondary outcomes included the peak serum creatinine level during the first 7 days after randomization, the maximum increase in creatinine level during ICU stay, receipt of new renal-replacement therapy, receipt and duration of treatment with vasoactive drugs, duration of mechanical ventilation in the ICU, length of ICU and hospital stays, and death from any cause during ICU stay, during hospital stay, and within 28 days after randomization. We also examined the primary outcome in six prespecified subgroups defined according to severity of illness before randomization, presence of sepsis, kidney injury, age, sex, and ICU admission after surgery.

STATISTICAL ANALYSIS

We estimated that a sample of 8800 patients would provide the trial with 90% power to detect an absolute difference of 2.9 percentage points in 90-day all-cause mortality from an estimated baseline mortality of 23%. Because the coronavirus disease 2019 pandemic disrupted recruitment and led to uncertainty over future recruitment and funding, in August 2020, the trial-management committee and sponsor, while unaware of the outcome data, decided to stop recruitment on December 31, 2020. We estimated that a sample of 5000 patients would provide the trial with 90% power to detect an absolute difference of 3.8 percentage points on the basis of the same assumption about baseline mortality (see the Supplementary Appendix and the statistical analysis plan[18]).

We exported the data to SAS Enterprise Guide, version 8.3 (SAS Institute), for analysis on an intention-to-treat basis. We used logistic regression to analyze the primary outcome of death from any cause within 90 days after randomization, with trial-group assignment as a fixed effect and ICU site as a random effect and without imputation of missing data. We performed adjusted analyses by adding sex, APACHE II score, presence of sepsis, and source of ICU admission (after surgery or other) as additional covariates. We converted odds ratios with 95% confidence intervals to adjusted risk differences with 95% confidence intervals using the Hummel and Wiseman method.[22]

Secondary analyses of the primary outcome included imputations for missing data according to "worst–best" and "best–worst" scenarios and multiple imputation. In the worst–best scenario, the worst outcome (i.e., dead at day 90) was assigned to all patients missing data on outcome in one trial group, and the best outcome (i.e., alive at day 90) was assigned to all patients missing data on outcome in the other trial group. The best–worst scenario corresponds to the reverse assignment of outcomes. We also repeated the primary analysis after sequentially (and cumulatively) excluding patients who received 500 ml or more of a trial fluid (other than the one they were assigned to receive) as open-label treatment

within 24 hours before enrollment, those who received 500 ml or more of a trial fluid (other than the one they were assigned to receive) as open-label treatment in the ICU after randomization, and those who received 500 ml or more of a trial fluid (other than the one they were assigned to receive) as open-label treatment either within 24 hours before enrollment or in the ICU after randomization. We further analyzed survival using a Cox model of time to death, with ICU site as a random effect. Post hoc, we conducted an inverse-probability-weighting analysis of the primary outcome to account for patients in the BMES group who received open-label saline after randomization (see the Supplementary Appendix),[23] and we analyzed whether our results crossed a futility boundary using an O'Brien and Fleming–type alpha-spending function.[24]

We analyzed continuous secondary outcomes and daily measures using repeated-measure linear mixed models. We analyzed durations and times to discharge as days alive and free of outcome (e.g., days alive and free of mechanical ventilation). We analyzed the time to live discharge after the index ICU and hospital admissions using cumulative-incidence functions, accounting for death as a competing risk, and using cause-specific Cox models with ICU site as a random effect. The independent data and safety monitoring committee conducted one planned interim analysis when a third of the patients in the original sample reached 90 days of follow-up.

RESULTS

TRIAL PATIENTS

A total of 5037 patients underwent randomization — 2515 were assigned to the BMES group and 2522 to the saline group. We did not have consent to assess the primary outcome in 62 patients (2.5%) in the BMES group and in 74 patients (2.9%) in the saline group, and 20 (0.8%) and 35 (1.4%) patients, respectively, were lost to follow-up. Consequently, data on the primary outcome were available for 2433 patients (96.7%) in the BMES group and 2413 patients (95.7%) in the saline group (Figs. S1 and S2 and Table S1 in the Supplementary Appendix).

The baseline characteristics of the patients were similar in the trial groups (Table 1 and Table S2a). The mean (±SD) age of the patients was 61.9±16.5 years, and 1948 patients (38.7%) were women. The median APACHE II score was 19 in both groups. Among 4899 patients with available data, 2216 (45.2%) were admitted to the ICU directly from the operating or recovery room, 3870 (79.0%) were receiving mechanical ventilation at the time of randomization, and 2071 (42.3%) had sepsis. The trial patients were representative of patients treated in the participating ICUs (Table S2b). Within 24 hours before randomization, the patients in the two groups had received similar amounts and types of intravenous fluid; 1360 of 2451 patients (55.5%) in the BMES group had received 500 ml or more of saline, and 567 of 2447 patients (23.2%) in the saline group had received 500 ml or more of BMES (Table S3).

FLUIDS ADMINISTERED AND TREATMENT EFFECTS

Trial fluid was administered in 4702 of 4896 (96.0%) patients — 2356 of 2450 patients (96.2%) in the BMES group and 2346 of 2446 patients (95.9%) in the saline group. The median duration of treatment with the assigned trial fluid was 6.0 days (interquartile range, 3.0 to 10.0) in both groups. The median volume of trial fluid received was 3.9 liters (interquartile range, 2.0 to 6.7) in the BMES group and 3.7 liters (interquartile range, 2.0 to 6.3) in the saline group (Fig. 1). After randomization, 1467 of 2330 patients (63.0%) in the BMES group received 500 ml or more of open-label saline, and 81 of 2324 patients (3.5%) in the saline group received 500 ml or more of the BMES (Table S4). Treatment with a trial fluid was discontinued prematurely in 102 of 2515 patients (4.1%) in the BMES group and in 127 of 2522 patients (5.0%) in the saline group. The most common reason for discontinuation was a clinical decision that included a change in the goal of treatment to palliation. Volumes of other intravenous fluids and blood products administered (Fig. S3), total fluid input (by any route) and output, and urine output (Fig. S4) did not differ significantly between the groups. Protocol deviations relating to fluid administration are listed in Table S5.

During the first 7 days after randomization, the daily mean heart rate, mean arterial pressure, and mean central venous pressure did not differ significantly between the groups (Fig. S5). Arterial blood pH was significantly higher and the serum chloride level was significantly lower among

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	BMES Group (N=2515)	Saline Group (N=2522)
Age — yr	61.7±16.4	62.1±16.5
Female sex — no./total no. (%)	937/2515 (37.3)	1011/2522 (40.1)
ICU admission source — no./total no. (%)		
Emergency department	834/2451 (34.0)	779/2448 (31.8)
Hospital floor, other hospital, or other ICU	524/2451 (21.4)	546/2448 (22.3)
Admitted after emergency surgery	657/2451 (26.8)	657/2448 (26.8)
Admitted after elective surgery	436/2451 (17.8)	466/2448 (19.0)
Median APACHE II score (IQR)†	19.0 (14.0–26.0)	19.0 (14.0–25.0)
Mechanical ventilation type — no./total no. (%)		
Invasive	1861/2451 (75.9)	1881/2448 (76.8)
Noninvasive	70/2451 (2.9)	58/2448 (2.4)
Receipt of new renal-replacement therapy — no./total no. (%)	47/2451 (1.9)	54/2448 (2.2)
Median time from ICU admission to randomization (IQR) — hr‡	2.0 (1.0–7.0)	2.0 (0.0–7.0)
Sepsis according to SIRS criteria — no./total no. (%)§	1048/2451 (42.8)	1023/2448 (41.8)
Sepsis according to Sepsis-3 criteria — no./total no. (%)§	1074/2450 (43.8)	1043/2447 (42.6)
Hospital admission for trauma — no./total no. (%)	201/2451 (8.2)	214/2448 (8.7)
Median SOFA score according to domain (IQR)¶		
Respiratory domain	2.0 (1.0–3.0)	2.0 (1.0–3.0)
Cardiovascular domain	3.0 (1.0–4.0)	3.0 (1.0–4.0)
Clinical measure‖		
Creatinine level — mg/dl	1.44±1.24	1.42±1.27
Heart rate — beats/min	92.1±23.4	92.9±23.4
Mean arterial pressure — mm Hg	73.2±12.8	73.8±13.0
Arterial blood pH	7.3±0.1	7.3±0.1
Base excess — mmol/liter	−4.2±5.6	−4.1±5.4
Serum lactate level — mmol/liter	2.7±2.5	2.7±2.4
Chloride level — mmol/liter	105.4±6.0	105.6±5.8

* Plus–minus values are means ±SD. The balanced multielectrolyte solution (BMES) group received Plasma-Lyte 148, and the saline group received 0.9% saline. To convert the values for creatinine to micromoles per liter, multiply by 88.4. ICU denotes intensive care unit, and IQR interquartile range.

† Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating an increased risk of death. Data were not available for 64 patients in the BMES group and 75 patients in the saline group.

‡ Data were not available for 64 patients in the BMES group and 74 patients in the saline group.

§ At the time the trial case-report form was designed, the diagnostic criterion for sepsis was systemic inflammatory response syndrome (SIRS) due to infection with accompanying organ dysfunction. During the trial, the Sepsis-3 criterion (infection with an accompanying 2-point increase in the Sequential Organ Failure Assessment [SOFA] score) became the accepted diagnostic criterion for sepsis. SOFA scores range from 0 to 24, as calculated from subscores ranging from 0 to 4 for each of six domains (respiratory, coagulation, liver, cardiovascular, central nervous system, and renal), with higher scores indicating more severe organ failure.

¶ Data on the SOFA respiratory-domain score were not available for 271 patients in the BMES group and 275 patients in the saline group. Data on the SOFA cardiovascular-domain score were not available for 71 patients in the BMES group and 79 patients in the saline group.

‖ Data were not available for 93 patients in the BMES group and 105 patients in the saline group regarding the creatinine level; for 68 and 77 patients, respectively, regarding the heart rate; for 75 and 83 patients, respectively, regarding the mean arterial pressure; for 235 and 250 patients, respectively, regarding the pH; for 263 and 270 patients, respectively, regarding the base excess; for 141 and 152 patients, respectively, regarding the serum lactate level; and for 102 and 112 patients, respectively, regarding the chloride level.

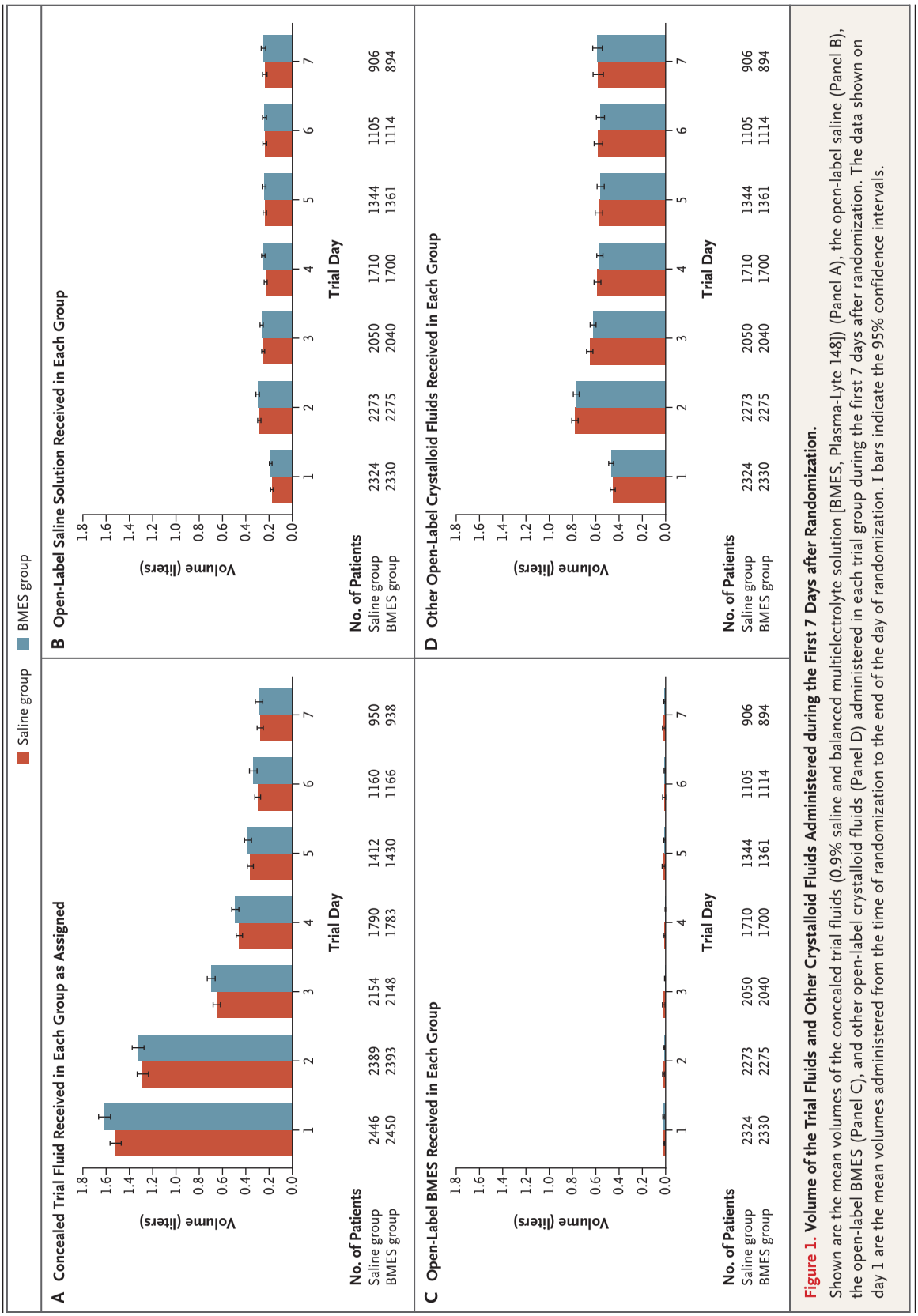
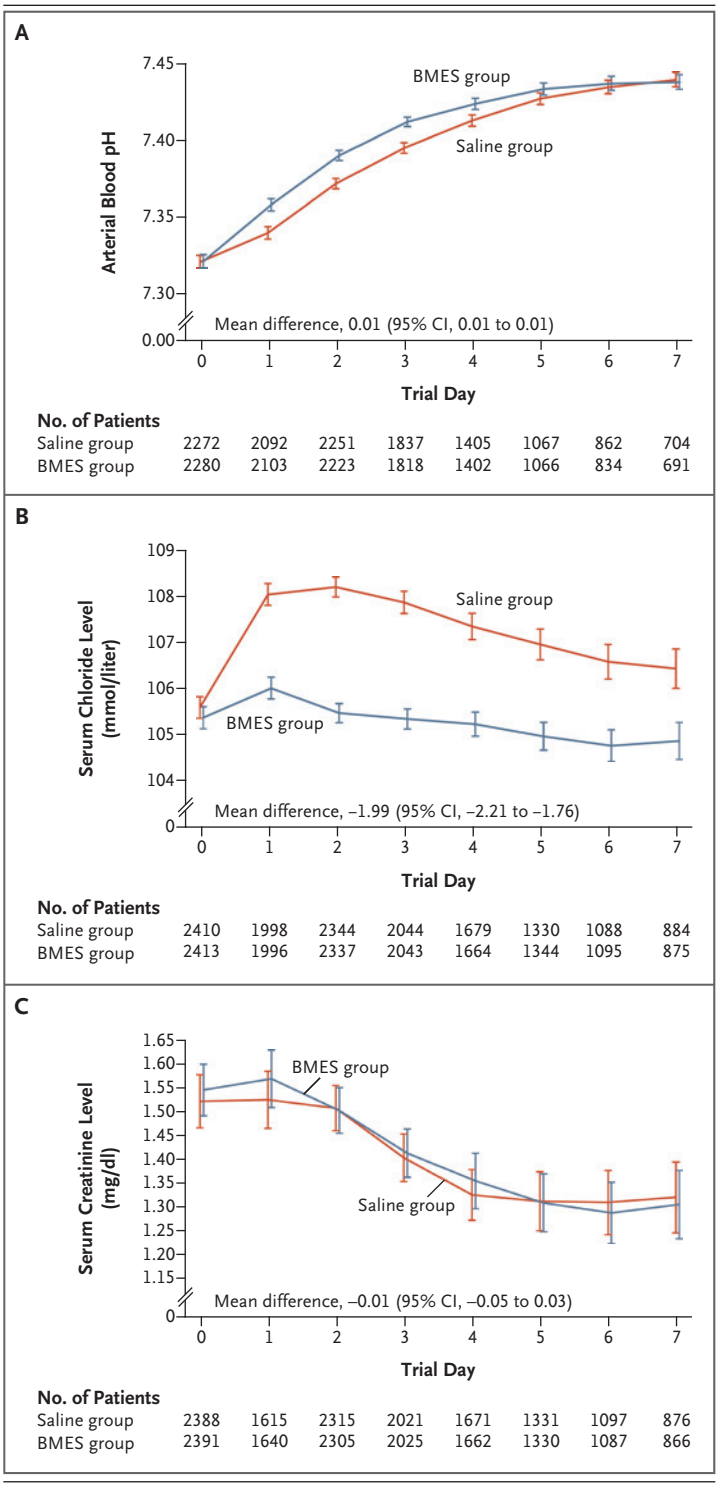


Figure 1. Volume of the Trial Fluids and Other Crystalloid Fluids Administered during the First 7 Days after Randomization.

Shown are the mean volumes of the concealed trial fluids (0.9% saline and balanced multielectrolyte solution [BMES, Plasma-Lyte 148]) (Panel A), the open-label saline (Panel B), the open-label BMES (Panel C), and other open-label crystalloid fluids (Panel D) administered in each trial group during the first 7 days after randomization. The data shown on day 1 are the mean volumes administered from the time of randomization to the end of the day of randomization. I bars indicate the 95% confidence intervals.

Figure 2. Changes in Arterial Blood pH and Serum Chloride and Creatinine Levels during the First 7 Days after Randomization.

Shown are the mean changes in arterial blood pH (Panel A), serum chloride level (Panel B), and serum creatinine level (Panel C) in each trial group during the first 7 days after randomization. Day 0 (baseline) data are the mean of the last values obtained before randomization; day 1 data are the mean of the last postrandomization levels recorded on the day of randomization. To convert the values for creatinine to micromoles per liter, multiply by 88.4. I bars indicate the 95% confidence intervals.



the patients in the BMES group than among those in the saline group (Fig. 2A and 2B). The serum creatinine level (Fig. 2C) and the levels of hemoglobin, lactate, and potassium (Fig. S6) did not differ significantly between the groups.

OUTCOMES

At 90 days, 530 of 2433 patients (21.8%) in the BMES group and 530 of 2413 patients (22.0%) in the saline group had died, for an absolute difference of −0.15 percentage points (95% confidence interval [CI], −3.60 to 3.30; P=0.90) and an odds ratio of 0.99 (95% CI, 0.86 to 1.14). Analyses with multiple imputation for missing data and with mortality assessed at different time points yielded similar results (Table 2). After adjustment for baseline risk factors, secondary analyses that excluded patients who received 500 ml or more of a trial fluid (other than the one they had been assigned to receive) as open-label treatment, as well as the post hoc analysis that used inverse probability weighting to account for the effect of the use of open-label saline in patients who were assigned to receive BMES, also yielded similar results (Table 2). Survival did not differ significantly between the two groups (Fig. 3A).

We detected no heterogeneity in the effect of fluid assignment on 90-day mortality in any subgroup (Fig. 3B). Place and cause of death did not differ significantly between the groups; most deaths occurred in the ICU and were due to distributive shock, hypoxic respiratory failure, cardiogenic shock, or neurologic injury (Table S6).

The maximum serum creatinine level during the first 7 days after randomization (Table 2 and Fig. 2) and the maximum increase in the serum creatinine level in the ICU were similar in the trial groups, as was the number of patients who received new renal-replacement therapy — 306 of 2403 patients (12.7%) in the BMES group and 310 of 2394 patients (12.9%) in the saline group,

Table 2. Trial Outcomes.*

Outcome	BMES Group (N=2515)	Saline Group (N=2522)	Odds Ratio (95% CI)	Absolute Difference (95% CI)†
Death from any cause within 90 days after randomization				
Primary analyses				
Unadjusted — no./total no. (%)	530/2433 (21.8)	530/2413 (22.0)	0.99 (0.86 to 1.14)	–0.15 (–3.60 to 3.30)‡
Adjusted§			0.99 (0.86 to 1.14)	–0.17 (–3.51 to 3.16)
Multiple imputation¶			0.99 (0.86 to 1.13)	–0.22 (–3.61 to 3.18)
Secondary analyses‖				
Secondary analysis 1			1.19 (0.96 to 1.46)	2.78 (–1.71 to 7.27)
Secondary analysis 2			0.94 (0.77 to 1.15)	–0.95 (–5.13 to 3.24)
Secondary analysis 3			1.06 (0.79 to 1.42)	0.91 (–4.65 to 6.47)
Inverse probability of treatment weighting — no./total no. (%)	176/858 (20.5)**	298/1574 (18.9)**	1.06 (0.88 to 1.28)	1.01 (–3.49 to 5.51)
Other mortality outcomes				
Death from any cause within 90 days after randomization while in the ICU — no./total no. (%)	395/2433 (16.2)	371/2413 (15.4)	1.07 (0.91 to 1.25)	0.89 (–2.03 to 3.81)
Death from any cause within 90 days after randomization while in the hospital — no./total no. (%)	503/2433 (20.7)	511/2413 (21.2)	0.97 (0.85 to 1.12)	–0.49 (–3.83 to 2.85)
Death from any cause within 28 days after randomization — no./total no. (%)	451/2433 (18.5)	445/2413 (18.4)	1.01 (0.87 to 1.17)	0.12 (–3.31 to 3.56)
Other binary outcomes				
Receipt of new renal-replacement therapy — no./total no. (%)	306/2403 (12.7)	310/2394 (12.9)	0.98 (0.83 to 1.16)	–0.20 (–2.96 to 2.56)
Receipt of vasoactive drugs — no./total no. (%)	2115/2453 (86.2)	2133/2448 (87.1)	0.92 (0.78 to 1.09)	–0.85 (–4.06 to 2.36)
Continuous outcomes				
Maximum creatinine level in the ICU during days 1 to 7 — mg/dl	1.76±1.44	1.75±1.43		0.01 (–0.04 to 0.06)
Maximum increase in creatinine level in the ICU — mg/dl	0.41±1.06	0.41±1.02		0.01 (–0.05 to 0.06)
Days alive and free of mechanical ventilation	68.3±33.4	68.2±33.4		0.06 (–1.79 to 1.91)
Days alive and free of vasoactive agents	69.9±32.9	69.9±32.7		0.03 (–1.80 to 1.85)
Days alive outside the ICU	65.3±32.8	65.3±32.8		0.05 (–1.77 to 1.87)
Days alive outside the hospital	52.9±31.7	52.3±31.5		0.62 (–1.15 to 2.38)

Adverse events		
Severe electrolyte or acid–base disturbance — no.	1	4
Cardiac arrest possibly related to trial fluid — no.	0	1
Drug precipitation in trial fluid — no.	2	0

* Plus–minus values are means ±SD.
† The differences shown are expressed as percentage points except for the differences in continuous outcomes.
‡ P=0.90.
§ The analysis was adjusted for sex, APACHE II score at randomization, presence of sepsis, and source of ICU admission (after surgery or other).
¶ Multiple imputation with 100 imputed data sets was performed to account for missing data on the primary outcome with the use of all baseline variables as predictors.
‖ Secondary analyses were adjusted for sex, APACHE II score at randomization, presence of sepsis, and source of ICU admission (postoperative or other). Secondary analysis 1 excluded patients who received 500 ml or more of a trial fluid (other than the one they were assigned to receive) as open-label treatment within 24 hours before enrollment. Secondary analysis 2 excluded patients who received 500 ml or more of a trial fluid (other than the one they were assigned to receive) as an open-label treatment in the ICU after randomization. Secondary analysis 3 excluded patients who received 500 ml or more of a trial fluid (other than the one they were assigned to receive) as open-label treatment either within 24 hours before enrollment or in the ICU after randomization.
** Data were weighted to account for patients in the BMES group who received open-label saline after randomization.

for an absolute difference of −0.2 percentage points (95% CI, −2.96 to 2.56).

The results regarding days alive and free of mechanical ventilation, days alive and free of renal-replacement therapy, days alive and free of vasoactive medication, days alive outside the ICU, and days alive outside the hospital were similar in the trial groups (Table 2 and Figs. S7 and S8). Measures of organ failure did not differ significantly between the groups (Figs. S9 and S10). In the post hoc analysis, our observed z score (−0.12) crossed the futility boundaries, which were between −0.57 and 0.57 when the number of patients recruited had reached 56% of the originally intended number (Fig. S11).

Adverse Events

The number of adverse and serious adverse reactions did not differ meaningfully between the trial groups. Details regarding adverse events are provided in Table 2 and Table S7.

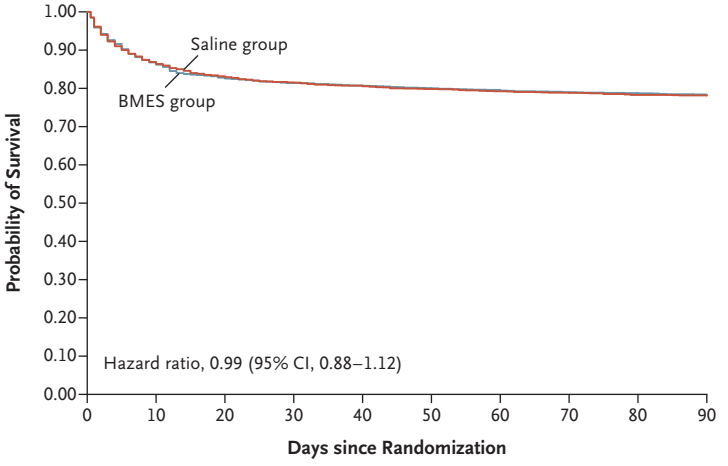
Discussion

This binational, randomized trial comparing a proprietary BMES with saline for fluid therapy in adult ICU patients did not show that 90-day mortality was lower with BMES. The use of saline resulted in a significantly higher serum chloride level and a lower pH than the use of BMES but had no significant effect on kidney function. Survival time, time in the ICU and in the hospital, and other markers of health care resource use were also similar in the trial groups.

The strengths of our trial include its conduct as a multicenter, double-blind trial conducted by experienced investigators.[1,3] We used a patient-centered primary outcome that was robust to adjusted analyses and multiple imputation. The trial patients received BMES or saline for a longer duration and in greater volume than in previous trials,[8,15] and the key biochemical measures that are hypothesized to mediate the adverse effects of saline differed significantly between the groups.[6,25-28] We followed a prespecified statistical analysis plan that included adjusted secondary analyses to examine the effects of open-label trial fluids and multiple imputation to account for missing data on the primary outcome.[18]

The limitations of our trial include a reduction in the size of the recruitment target and unavailable data on the primary outcome for

A Kaplan–Meier Estimates of the Probability of Survival



No. of Patients										
BMES group	2446	2119	2019	1983	1964	1949	1937	1922	1916	1906
Saline group	2430	2109	2015	1973	1952	1929	1913	1904	1890	1884

B Subgroup Analysis of Death from Any Cause

Subgroup	BMES Group	Saline Group	Odds Ratio (95% CI)
	no. of events/total no. (%)		
Age			
<65 yr	184/1250 (14.7)	188/1207 (15.6)	0.93 (0.74–1.16)
≥65 yr	346/1183 (29.2)	342/1206 (28.4)	1.06 (0.88–1.26)
Sex			
Male	328/1531 (21.4)	323/1437 (22.5)	0.94 (0.79–1.12)
Female	202/902 (22.4)	207/976 (21.2)	1.09 (0.87–1.35)
Kidney injury			
Yes	160/468 (34.2)	155/451 (34.4)	0.98 (0.74–1.29)
No	361/1934 (18.7)	370/1931 (19.2)	0.97 (0.83–1.15)
Sepsis			
Yes	276/1068 (25.8)	265/1026 (25.8)	1.01 (0.83–1.23)
No	254/1362 (18.6)	265/1386 (19.1)	0.97 (0.80–1.17)
Admitted from surgery			
Yes	171/1087 (15.7)	179/1109 (16.1)	0.97 (0.77–1.22)
No	359/1344 (26.7)	351/1304 (26.9)	0.99 (0.84–1.18)
APACHE II score			
<25	287/1753 (16.4)	275/1739 (15.8)	1.05 (0.88–1.26)
≥25	243/678 (35.8)	255/673 (37.9)	0.90 (0.72–1.12)

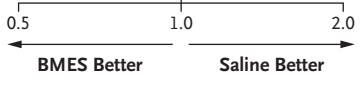


Figure 3. Probability of Survival and Odds Ratios for Death According to Trial Group.

Panel A shows Kaplan–Meier estimates of the probability of survival, which were similar among the patients in the BMES group and among those in the saline group (hazard ratio for death from any cause, 0.99; 95% CI, 0.88 to 1.22). Panel B shows the odds ratios with 95% confidence intervals for death from any cause within 90 days after randomization in six prespecified subgroups. The Acute Physiology and Chronic Health Evaluation (APACHE) II score ranges from 0 to 71, with higher scores indicating more severe organ dysfunction.

some patients. Nevertheless, we believe that our findings are reliable, because the data for our primary outcome crossed a conservative futility boundary that made it unlikely that further recruitment would have altered our findings. More than half the patients in the BMES group received 500 ml or more of saline in the ICU, predominantly for the delivery of medications

that have not been tested for compatibility with BMES; it is possible that this may have attenuated a protective effect of BMES, but the results of our secondary analyses and post hoc inverse-probability-weighting analysis do not support this contention. In addition, we did not control or record all fluid that the patients received outside the ICU. We did not examine the effects of BMES as compared with saline in patients with traumatic brain injury because we considered saline or a fluid with equivalent tonicity to be indicated in such patients.[29,30]

Our results are consistent with the findings of the Balanced Solution versus Saline in Intensive Care Study (BaSICS),[31] another large, multicenter, double-blind trial that compared Plasma-Lyte 148 with saline in ICU patients, and the 0.9% Saline versus Plasma-Lyte 148 for ICU Fluid Therapy trial, a smaller double-blind, cluster-crossover trial that compared the same fluids.[15] Our results appear to be inconsistent with those of the Isotonic Solutions and Major Adverse Renal Events Trial (SMART), an open-label, cluster-crossover trial conducted at a single medical center in the United States.[8] In SMART, the use of saline increased the proportion of patients who met the criteria for the composite outcome of a major adverse kidney event at 30 days (MAKE 30).[8] However, the values obtained for the individual components of MAKE 30 (30-day mortality, change in serum creatinine level, and the proportion of patients treated with dialysis) did not show significant increases among those treated with saline.[8] A secondary analysis in SMART showed that the use of saline in patients with sepsis increased mortality,[10] although we found no such effect in our trial.

Our data suggest that the use of either BMES or saline for fluid therapy in the ICU resulted in similar outcomes, but our results are also consistent with an increase or decrease of approximately 3 percentage points in the risk of death or receipt of new renal-replacement therapy. The results of an updated meta-analysis that included our data suggest that there is a high probability that the use of balanced salt solutions reduces mortality among critically ill adults, with the possibility of important subgroup effects (now reported in *NEJM Evidence*).[32] Therefore, individual patient characteristics and other factors, including cost and availability of the fluids, and drug compatibility may determine which fluids are used. The use of balanced solutions may confer benefits in specific patient populations, such as those with diabetic ketoacidosis in whom its use may result in a more rapid resolution of acidosis and may shorten the duration of treatment in the ICU and hospital.[33,34] Further trials are needed to confirm these benefits and to establish whether balanced solutions improve outcomes in patients with other metabolic or electrolyte disturbances. Data from BaSICS suggest that Plasma-Lyte 148 may be harmful in patients with traumatic brain injury[31] and that saline should remain the fluid of choice for such patients. Further evaluation of the safety of balanced solutions in patients with nontraumatic acute brain injuries is needed.

In our trial involving a heterogeneous population of critically ill adults, we found no evidence that the use of BMES in preference to saline in the ICU resulted in a lower all-cause mortality or risk of acute kidney injury. However, the confidence intervals around our results encompass a modest increase or decrease in either of these outcomes with the use of BMES.

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

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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