RESEARCH REPORT

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Lactated Ringer's or Normal Saline for Initial Fluid Resuscitation in Sepsis-Induced Hypotension

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OBJECTIVES: To assess whether initial fluid resuscitation with lactated Ringer's solution compared with 0.9% saline is associated with improved clinical outcomes in patients with sepsis-induced hypotension.

DESIGN: Secondary analysis of the randomized controlled Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) trial.

SETTING: ICUs and emergency departments in 60 U.S. centers from March 2018 to January 2022.

PATIENTS: Participants from the CLOVERS trial. Adult patients with a suspected or confirmed infection and hypotension caused by sepsis.

INTERVENTIONS: Participants received 1–3 L of crystalloid fluid for initial fluid resuscitation before randomization. In this analysis, participants were categorized into a lactated Ringer's group and a 0.9% saline group based on the fluid type predominantly used for the initial fluid resuscitation (i.e., ≥ 95% of pre-randomization fluid).

MEASUREMENTS AND MAIN RESULTS: Of 1563 participants with sepsis-induced hypotension included in the CLOVERS trial, 622 (39.8%) received lactated Ringer's solution and 690 (44.1%) received 0.9% saline as solution for the initial fluid bolus. Death before discharge home by day 90 occurred in 76 of 622 participants (12.2%) in the lactated Ringer's group and in 110 of 690 participants (15.9%) in the 0.9% saline group, resulting in an adjusted hazard ratio of 0.71 (95% CI, 0.51–0.99; $p = 0.043$). Patients receiving lactated Ringer's solution had more hospital-free days at 28 days than those receiving 0.9% saline (16.6 ± 10.8 vs. 15.4 ± 11.4, respectively; adjusted mean difference, 1.6 d [95% CI, 0.4–2.8 d; $p = 0.009$]). Treatment with 0.9% saline was associated with higher levels of serum chloride and decreased levels of serum bicarbonate.

CONCLUSIONS: Initial fluid resuscitation with lactated Ringer's solution, compared with 0.9% saline, might be associated with improved survival in patients with sepsis-induced hypotension.

KEYWORDS: acidosis; balanced crystalloid; hyperchloremia; multibalanced

Fluid resuscitation is a cornerstone treatment in the management of sepsis. The controversy of early resuscitation fluid choice and its effect on outcome remains a debated question (1, 2). The use of 0.9% sodium chloride (saline) has been common practice and is highly prevalent in the ICU (3). However, recent data suggests potential harm, such as hyperchloremic metabolic acidosis, renal vasoconstriction, and acute kidney injury, associated with its use (4). Previously, balanced crystalloids (e.g., lactated Ringer's solution) or 0.9% saline were equally recommended, but this changed with the 2021 Surviving Sepsis Campaign (SSC) guidelines favoring balanced crystalloids for initial fluid resuscitation in sepsis (5). Evidence for this recommendation was based on studies

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KEY POINTS

Question: Is lactated Ringer's solution, as compared with 0.9% saline, for initial fluid resuscitation associated with improved clinical outcomes in patients with sepsis-induced hypotension?

Findings: In the Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) trial population, death before discharge home by day 90 occurred in 12% of participants in the lactated Ringer's group and in 16% of participants in the 0.9% saline group (adjusted hazard ratio, 0.71; 95% CI, 0.51–0.99).

Meaning: In line with the 2021 Surviving Sepsis Campaign guidelines, our results suggest that initial fluid resuscitation with lactated Ringer's solution, compared with 0.9% saline, might be associated with improved outcome in patients with sepsis-induced hypotension.

investigating extended treatment periods exceeding the initial fluid resuscitation. The value of using balanced crystalloids specifically for initial fluid resuscitation has not been adequately studied. Hence, in contrast to previous literature, the present study investigated the fluid choice for the initial 1–3 L of fluid resuscitation in patients with sepsis-induced hypotension, irrespective of the subsequent fluid type used.

The Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) trial randomized participants with sepsis-induced hypotension to an early restrictive treatment strategy or liberal fluid treatment strategy and was unable to detect a significant difference in mortality (6). We used the CLOVERS trial data to investigate whether initial fluid resuscitation with lactated Ringer's solution is associated with improved survival as compared with 0.9% saline.

METHODS

Design

This secondary analysis of the CLOVERS trial investigated whether initial fluid resuscitation with balanced crystalloid fluids (lactated Ringer's solution) compared with 0.9% saline was associated with improved outcomes in sepsis-induced hypotension. The design and results of the original CLOVERS trial have been published previously (6, 7). Because the two treatment strategies (early restrictive and liberal fluid management) yielded similar outcomes, patients were pooled irrespective of their group assignment for this secondary analysis. Data for this secondary analysis were obtained from the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center. Review by an institutional review board (Ethics Committee of the Medical University of Vienna) was not required because this project did not fall under the board's guidelines as human subjects research.

Participants

In the CLOVERS trial, participants were randomly assigned to either a restrictive fluid strategy (prioritizing vasopressors and lower IV fluid volumes) or a liberal fluid strategy (prioritizing higher volumes of IV fluids before vasopressor use) for a 24-hour period. Randomization occurred within 4 hours after a patient met the criteria for sepsis-induced hypotension refractory to initial fluid resuscitation (pre-randomization) with 1–3 L of IV fluid, including prehospital administration of fluid by emergency medical services. In the present analysis, we investigated whether initial fluid resuscitation (corresponding to fluids administered before randomization) with lactated Ringer's solution as compared with 0.9% saline was associated with improved clinical outcomes. Patients were divided into the lactated Ringer's group or the 0.9% saline group. Patients were included in this analysis if the administered pre-randomization fluid was greater than or equal to 95% lactated Ringer's solution or 0.9% saline. Patients receiving a combination of fluids were excluded.

Outcomes

The primary outcome was death from any cause before discharge home by day 90. Secondary outcomes included 28-day measures of the number of days free from ventilator use, days free from vasopressor use, days out of the ICU, and days out of the hospital. We also assessed the occurrence rate of acute kidney injury, defined as a short-term increase in serum creatinine by greater than or equal to 0.3 mg/dL or an greater than or equal to 1.5-fold increase in creatinine levels (**Table S1**, http://links.lww.com/CCM/H687). An exploratory comparison of the change in serum biomarkers

(chloride, bicarbonate, lactate, and creatinine) within the first 72 hours of randomization was performed.

Statistical Analysis

The primary endpoint was analyzed using a Cox proportional hazard model. No violation of the proportional hazard assumptions was found. The primary analysis was based on a multiple Cox regression model adjusted for the covariates sex, age-adjusted Charlson Comorbidity Index, Sequential Organ Failure Assessment (SOFA) score, vasopressor use, acute respiratory distress syndrome, assigned treatment protocol (early restrictive vs. liberal fluid group), mean arterial blood pressure, amount of lactated Ringer's solution and 0.9% saline used in the 24 hours after randomization, and a propensity score for each patient's probability of receiving lactated Ringer's solution rather than 0.9% saline. Additional information on the statistical adjustment and the propensity scores are provided in **Item S1** (http://links.lww.com/CCM/H687). We performed a sensitivity analysis by sequentially omitting each covariate from the adjusted model and by adding chronic kidney disease as independent covariate.

Secondary endpoints included the number of exposure-free days up to day 28 for several outcomes. Group comparisons were performed using mean differences in exposure-free days adjusted for the same covariates as the Cox regression model.

Due to the exploratory nature of this analysis, CIs were not adjusted for multiple comparisons.

RESULTS

Participants

Of the 1563 participants included in the CLOVERS trial, 622 (39.8%) received lactated Ringer's solution and 690 (44.1%) received 0.9% saline for the initial fluid bolus (**Fig. S1**, http://links.lww.com/CCM/H687). Baseline characteristics were comparable between the two groups (**Table S2**, http://links.lww.com/CCM/H687). Patients receiving lactated Ringer's solution were slightly younger (median, 58 [IQR, 47–68] vs. 62 [52–71]) than patients receiving 0.9% saline. Comorbidities were similar between the two groups, with the exception of chronic kidney disease, which was more prevalent in the 0.9% saline group. No significant differences were observed for the SOFA score at randomization (3 [1–5] vs. 3 [1–5]), amount of fluid for initial pre-randomization bolus (mean ± SD, 1922 ± 601 vs. 1966 ± 621 mL), vasopressor use at randomization (17.2% vs. 17.7%), and serum lactate levels (2.2 mmol/L [1.4–3.4 mmol/L] vs. 2.2 mmol/L [1.5–3.4 mmol/L]). Fluid volumes and balance by treatment group are shown in **Table S3** (http://links.lww.com/CCM/H687).

Outcomes

Death before discharge home by day 90 occurred in 76 of 622 participants (12.2%) in the lactated Ringer's group and in 110 of 690 participants (15.9%) in the 0.9% saline group (adjusted hazard ratio [HR], 0.71; 95% CI, 0.51–0.99; $p = 0.043$; **Fig. 1**). The adjusted HR of the primary outcome was similar but did not remain statistically significant after omitting sex (0.72 [95% CI, 0.55–1.0]), the Charlson Comorbidity Index (0.74 [95% CI, 0.53–1.03]), the Glasgow Coma Scale (0.75 [95% CI, 0.54–1.04), the amount of lactated Ringer's solution and 0.9% saline after randomization (0.74 [95% CI, 0.55–1.01]), and blood pressure (0.73 [95% CI, 0.53–1.01]) from the model. Further, the adjusted HR did not remain statistically significant after adding chronic kidney disease as independent covariate (0.73 [95% CI, 0.52–1.01]) (**Table S4**, http://links.lww.com/CCM/H687).

Table 1 shows the group comparison of the secondary endpoints. Patients receiving lactated Ringer's solution had more hospital-free days at 28 days than those receiving 0.9% saline (16.6 ± 10.8 vs. 15.4 ± 11.4 d, respectively), resulting in an adjusted mean difference of 1.6 days (95% CI, 0.4–2.8; $p = 0.009$). There were no other statistically significant group differences in the secondary endpoints.

Acute kidney injury within 7 days occurred in 57 (9.2%) in the lactated Ringer's group and in 77 (11.2%) of the 0.9% saline group (adjusted odds ratio, 0.77; 95% CI, 0.5–1.2; $p = 0.206$).

Treatment with 0.9% saline was associated with higher levels of serum chloride and decreased levels of serum bicarbonate (**Fig. S2**, http://links.lww.com/CCM/H687).

DISCUSSION

In this analysis of the CLOVERS trial, initial fluid resuscitation with lactated Ringer's solution as compared with 0.9% saline was associated with a reduced 90-day mortality and more hospital-free days at 28 days.

Current SSC guidelines suggest balanced crystalloids for fluid resuscitation in patients with sepsis, including the

initial fluid resuscitation phase of 30mL/kg within the first 3 hours. The suggestion to use balanced crystalloids is supported by a secondary analysis of the Isotonic Solutions and Major Adverse Renal Events Trial (SMART) trial, which showed benefits with balanced crystalloids compared with 0.9% saline in patients with sepsis (8). The importance of early resuscitation fluid choice is shown in a secondary analysis of the Balanced Solutions in Intensive Care Study (BaSICS), which found a survival benefit with balanced crystalloids as compared with 0.9% saline in critically ill patients who exclusively received balanced crystalloids before trial enrollment (9). Furthermore, the benefit of balanced crystalloids may also be dependent on the timing of treatment initiation (10). However, no studies investigated the relevance of the type of crystalloid fluid used specifically for the initial fluid resuscitation in sepsis. In previous trials, comparing balanced crystalloids to 0.9% saline in critically ill patients (including the SMART trial), fluid treatment regimens lasted for a minimum of 24 hours up to the length of the ICU stay, which precludes the assessment of the initial resuscitation only.

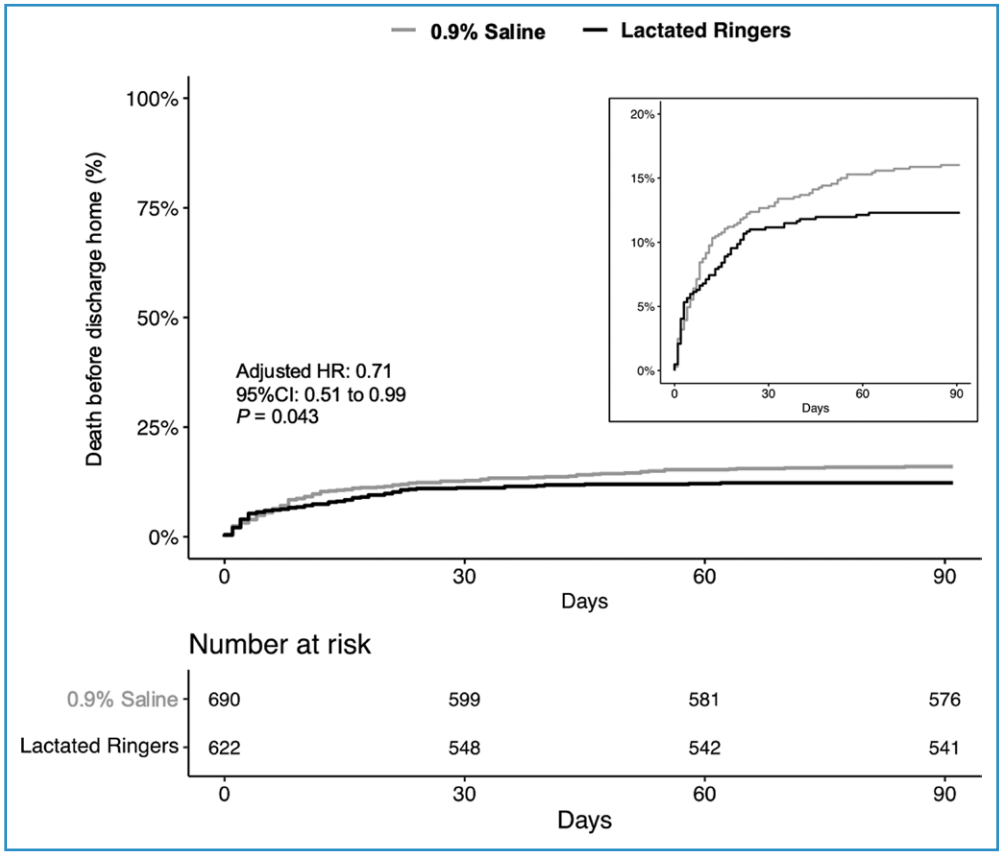

Figure 1. Kaplan-Meier curves of the time to death before discharge home by day 90 between the lactated Ringer's solution group and the 0.9% saline group. HR = hazard ratio.

TABLE 1.
Comparison of Secondary Endpoints Between the Lactate Ringer's and 0.9% Saline Group

Outcome	Lactated Ringer's Group	0.9% Saline Group	Adjusted Mean Difference (95% CI)	Adjusted *p*
n	622	690		
Days free from organ support at 28 d, mean ± SD	24.2 (8.5)	23.5 (8.9)	0.6 (−0.4 to 1.5)	0.2277
Days free from ventilator use at 28 d, mean ± SD	23.7 (9.7)	22.7 (10.5)	0.9 (−0.2 to 2.0)	0.1228
Days free from renal replacement therapy at 28 d, mean ± SD	24.4 (9.3)	23.8 (10.0)	0.7 (−0.5 to 1.8)	0.2486
Days free from vasopressor use at 28 d, mean ± SD	22.3 (8.8)	21.5 (9.5)	0.7 (−0.3 to 1.7)	0.1941
Days out of the ICU by day 28, mean ± SD	23.3 (8.6)	22.5 (9.0)	0.5 (−0.4 to 1.5)	0.2592
Days out of the hospital by day 28, mean ± SD	16.6 (10.8)	15.4 (11.4)	1.6 (0.4–2.8)	0.0088

While this study investigated the difference in 90-day mortality, the relatively early timing of separation of the Kaplan-Meier curves may support the causal relationship of type of fluid used for early fluid resuscitation and survival. As potential mechanistic intermediates, higher levels of chloride and an initial drop in bicarbonate could suggest metabolic acidosis associated with 0.9% saline. As fluid resuscitation for sepsis-induced hypotension often begins in a prehospital setting, the choice of fluid type by emergency physicians and paramedics might be of significance. In clinical practice, the choice of the appropriate crystalloid fluid may ultimately depend on individual electrolyte disorders.

Our study has limitations. Because this is a secondary analysis, our findings carry a risk for false positives (type I error). Although the analysis was adjusted for several covariates, residual confounding cannot be excluded. The prevalence of chronic kidney disease was significantly higher in the 0.9% saline group compared with the lactated Ringer's group. However, the primary analysis was adjusted for the Charlson Comorbidity Index, which included chronic kidney disease. In our sensitivity analysis, omitting sex, the Charlson Comorbidity Index, the Glasgow Coma Scale, blood pressure and the amount of lactated Ringer's solution and 0.9% saline after randomization, and adding chronic kidney disease as an independent covariate (outside of the Charlson Comorbidity Index) yielded similar estimates but did not reach statistical significance. Considering our results were not robust to several variations in the model, our study is mainly hypothesis generating.

In conclusion, our results suggest that initial fluid resuscitation with lactated Ringer's solution, compared with 0.9% saline, might be associated with improved survival in patients with sepsis-induced hypotension. This is in line with the suggestions of current SSC guidelines and supports the use of lactated Ringer's solution for initial fluid resuscitation.

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