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Lactated Ringer vs Normal Saline Solution During Sickle Cell Vaso-Occlusive Episodes

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IMPORTANCE Sickle cell disease (SCD), a clinically heterogenous genetic hemoglobinopathy, is characterized by painful vaso-occlusive episodes (VOEs) that can require hospitalization. Patients admitted with VOEs are often initially resuscitated with normal saline (NS) to improve concurrent hypovolemia, despite preclinical evidence that NS may promote erythrocyte sickling. The comparative effectiveness of alternative volume-expanding fluids (eg, lactated Ringer [LR]) for resuscitation during VOEs is unclear.

OBJECTIVE To compare the effectiveness of LR to NS fluid resuscitation in patients with SCD and VOEs.

DESIGN, SETTING, AND PARTICIPANTS This multicenter cohort study and target trial emulation included inpatient adults with SCD VOEs who received either LR or NS on hospital day 1. The Premier PINC AI database (2016-2022), a multicenter clinical database including approximately 25% of US hospitalizations was used. The analysis took place between October 6, 2023, and June 20, 2024.

EXPOSURE Receipt of LR (intervention) or NS (control) on hospital day 1.

MAIN OUTCOME AND MEASURES The primary outcome was hospital-free days (HFDs) by day 30. Targeted maximum likelihood estimation was used to calculate marginal effect estimates. Heterogeneity of treatment effect was explored in subgroups.

RESULTS A total of 55 574 patient encounters where LR (n = 3495) or NS (n = 52 079) was administered on hospital day 1 were included; the median (IQR) age was 30 (25-37) years. Patients who received LR had more HFDs compared with those who received NS (marginal mean difference, 0.4; 95% CI, 0.1-0.6 days). Patients who received LR also had shorter hospital lengths of stay (marginal mean difference, −0.4; 95% CI, −0.7 to −0.1 days) and lower risk of 30-day readmission (marginal risk difference, −5.8%; 95% CI, −9.8% to −1.8%). Differences in HFDs between LR and NS were heterogenous based on fluid volume received: among patients who received less than 2 L, there was no difference in LR vs NS; among those who received 2 or more L, LR was superior to NS.

CONCLUSION AND RELEVANCE This cohort study found that, compared with NS, LR had a small but significant improvement in HFDs and secondary outcomes including 30-day readmission. These results suggest that, among patients with VOEs in whom clinicians plan to give volume resuscitation fluids on hospital admission, LR should be preferred over NS.

Invited Commentary

Supplemental content

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Sickle cell disease (SCD), a clinically heterogenous genetic hemoglobinopathy that causes abnormal form of hemoglobin, is characterized by chronic hemolytic anemia, dysregulated inflammation, and recurrent episodes of vaso-occlusion.[1] Vaso-occlusive episodes (VOEs) are a primary cause of morbidity and mortality in patients with SCD and can precipitate hospitalizations for pain management. VOEs may be complicated by hypovolemia (due to reduced oral intake, insensible losses, and hyposthenuria) and metabolic acidosis, both of which may exacerbate erythrocyte sickling.[2-5] Thus, it is important to provide adequate fluid resuscitation that minimizes risk for metabolic acidosis in patients with VOEs. Among all hospitalized patients (not specifically those with SCD), emerging evidence suggests that fluid resuscitation with balanced (eg, lactated Ringer [LR]) rather than unbalanced (eg, normal [0.9%] saline [NS]) decreases risks of hyperchloremic metabolic acidosis[6] and potentially mortality.[7] Moreover, NS may promote microvascular environments that predispose to erythrocyte sickling.[8,9] However, the comparative effectiveness of LR vs NS in patients with SCD remains unclear, patients with VOEs predominantly receive NS,[10] and clinical decision support resources recommend treatment with NS.[9]

In this study, we used a large multicenter US cohort and target trial emulation[11] to compare the effectiveness of LR to NS resuscitation in patients with SCD hospitalized for VOEs.

Key Points

Question What is the comparative effectiveness of lactated Ringer solution vs normal saline for fluid resuscitation in inpatients with sickle cell disease and vaso-occlusive episodes?

Findings In this multicenter retrospective cohort study, use of lactated Ringer solution was associated with more hospital free-days, shorter hospital length of stay, and lower 30-day readmission risk compared with normal saline.

Meaning In a multicenter retrospective cohort study and target trial emulation, patients with sickle cell disease and vaso-occlusive episodes who received lactated Ringer solution had small but significant improvements in outcomes compared with patients who received normal saline.

Methods

Target Trial Emulation

Target trial emulation is a methodologic framework where observational comparative effectiveness studies are designed to mimic hypothetical randomized clinical trials (RCTs).[11] Use of target trial emulation helps to minimize common pitfalls of observational design including selection and immortal time biases.[12-14] In this study, we sought to emulate a clinical trial that would (1) enroll patients with SCD on the day of admission to the hospital for management of a VOE, (2) randomize patients immediately to receive resuscitation with LR or NS, and (3) follow-up patients from enrollment to hospital discharge or for 30 days (whichever came first) to compare the average number of hospital-free days (HFDs) between treatments (eTable 1 in Supplement 1). This study was designated not human participants research by Boston University's institutional review board (#H-41795). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for reporting observational studies.[15] The analysis took place between October 6, 2023, and June 20, 2024.

Data Source

We used the Premier PINC AI database[16] (January 1, 2016-September 30, 2022), an enhanced claims database including approximately 25% of US hospitalizations. Included hospitals are from all 4 US Census regions and have characteristics similar to those from the American Hospital Association Database.[16] The database contains claims data and hospital day-indexed billing information with minimal missing data (<0.01% of fields are missing).[17] Data are granular to the level of the calendar day (12:00 AM to 11:59 PM) and includes data from admission to discharge but not prehospitalization (eg, emergency department) or posthospitalization data.

Study Population

Included patients were adults (age ≥18 years) with *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnoses for SCD and a VOE (designated as present on admission and the primary diagnosis). We limited the cohort to those patients who received LR or NS (using hospital charge codes for 500- to 1000-mL bags) on hospital calendar day 1; patients receiving both fluid types on hospital day 1 were excluded. We limited to fluid use on hospital day 1 because we were interested in early fluid administration given for resuscitation, not for maintenance (eg, half NS given continuously later in the hospital course). We excluded patients who were transferred from outside hospitals (because patients' clinical courses prior to admission were unknown) and those who received kidney replacement therapy on hospital day 1 (consistent with prior clinical trials of balanced vs unbalanced fluid[18] and because putative mechanisms of balanced fluid benefits related to acute kidney injury[19] are unlikely to occur in patients receiving kidney replacement therapy). We also excluded hospitals with less than 25 included encounters to facilitate model convergence. The unit of analysis was the hospital admission encounter. Inclusion/exclusion criteria are shown in eTable 2 in Supplement 1.

Exposure and Outcomes

The intervention was receipt of LR on hospital day 1 and the comparator was receipt of NS on hospital day 1. The primary outcome was HFDs by day 30 (HFD; a measure of hospital length of stay that accounts for the competing risk of death).[20] We selected HFDs as the primary outcome to mimic the primary outcome in a large trial comparing balanced to unbalanced fluid in all hospitalized patients,[21] and because longer lengths of stay may be a downstream consequence of in-hospital complications of SCD VOEs such as prolonged need for intravenous pain control medication, blood transfusions, infection and acute chest syndrome. HFDs were calculated as

30 minus the hospital length of stay in calendar days of the index hospitalization (up to a max of 30 days) with patients who died in the hospital and patients discharged after 30 days assigned 0 free days. Thus, lower HFDs represent patients with longer hospital lengths of stay and/or higher likelihoods of in-hospital death. Subsequent hospitalizations were not included in HFD calculations.

Secondary outcomes were (1) intravenous opioid-free days by day 30, (2) blood transfusion–free days by day 30, (3) organ support-free (kidney replacement therapy, invasive mechanical ventilation, or vasopressor use) days by day 30, (4) hospital mortality by day 30, (5) intravenous diuretic use by day 30 (a surrogate for hypervolemia), (6) 30-day readmission, and (7) hospital length of stay by day 30. Outcomes were measured starting on hospital day 1. Exposure and outcome definitions are shown in eTable 2 in Supplement 1.

Covariables

Guided by directed acyclic graphs (eFigure 1 in Supplement 1), we included the following covariables in models: demographics, measures of comorbidity (including kidney failure, congestive heart failure, and pulmonary circulation disorders),[22,23] and acute organ dysfunction present on admission,[24,25] hydroxyurea use on hospital day 1, care location on hospital day 1 (wards, intermediate care, intensive care), discharge year, hemoglobin SS genotype (HbSS) defined based on *ICD-10* codes, and an indicator variable for the hospital of admission to account for institutional-specific practices, environment, and outcomes (eTable 2 in Supplement 1).

Statistical Analysis

Prior to modeling, we summarized covariables across exposure groups using median (IQR) and counts (%) and assessed balance using absolute standardized means differences (SMDs; SMDs <0.1 suggest similarity). We summarized fluid practices across hospitals using medians, IQRs, and ranges. We used targeted maximum likelihood estimation (TMLE; R package tmle; R Foundation[26]), a doubly robust ensemble machine learning approach that provides semiparametric, locally efficient substitution estimators to identify associations between fluid type and outcomes.[27] TMLE yields average treatment effects (ATEs), which can be conceptualized as average differences in outcomes in the population if everyone was treated with LR vs if everyone was treated with NS. Because in actuality patients only receive a single treatment, TMLE uses models to estimate what the outcome would have been for each patient assuming that they had been treated with LR (scenario 1) vs with NS (scenario 2). The ATE is then calculated as the average estimated outcome in scenario 1 minus that in scenario 2. The TMLE algorithm follows the following steps: (1) model the outcome using the treatment variable and all covariables to predict each patient's outcome under the 2 treatment scenarios; (2) model the probability of the observed treatment using all covariables; and (3) use information from the treatment probability model to update each patient's outcome in step 1 to optimize the bias-variance tradeoff and then take the average difference between scenarios across patients to calculate the ATE. Unlike simple propensity score-based methods, TMLE is doubly robust, that is, if either the model for the outcome or for the treatment are correctly specified, the results will be valid. Moreover, unlike traditional parametric models that rely on strict assumptions about the relationships between model variables, TMLE uses ensemble machine learning[28] that combines many models (generalized linear models, least absolute shrinkage and selection operator models, and regularized gradient boosting models) that can account for complex, nonlinear relationships. Cross-validation of the outcome model was used to minimize overfitting. Statistical inference was based on influence curves and accounted for repeat admissions per patient in the id argument.[26] Results were reported as marginal mean differences (95% CIs) for continuous and marginal risk differences (95% CI) for dichotomous outcomes.[26,29]

In sensitivity analyses, we (1) limited to 1 random admission per patient, (2) limited to patients who remained hospitalized on the day after exposure, and (3) excluded patients who received less than 0.5 L or more than 10 L of resuscitative fluid on day 1 and included fluid volume received in TMLE models.

We examined heterogeneity of treatment effect in subgroups based on (1) HbSS genotype, (2) admission to an intensive care or stepdown unit, (3) receipt of 2 or more L of fluid on hospital day 1,[21] and (4) diagnosis of acute kidney dysfunction present on admission.[25] We tested for interaction between subgroups as previously described.[30]

For all comparisons, α was set at .05; all comparisons other than for the primary outcome should be considered hypothesis-generating. There were no missing data that required imputation. R statistical software (version 4.0.5; R Foundation) was used for analyses; eAppendix in Supplement 1 contains representative analysis code.

Results

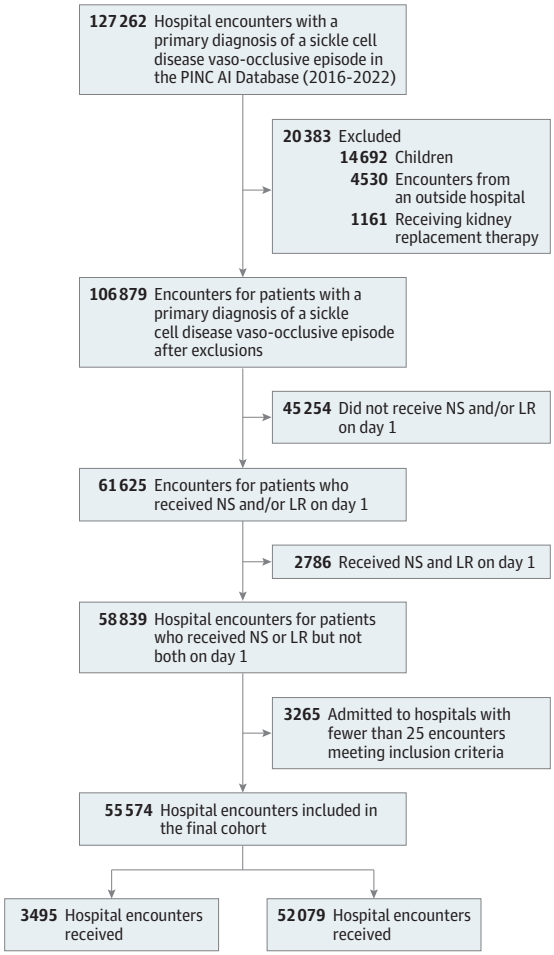
Study Population and Baseline Characteristics

Among 127 262 hospitalized encounters for patients with SCD and VOEs in PINC AI, 61 625 received LR or NS on hospital day 1. A total of 55 574 patient encounters (15 798 patients) were included in the final study cohort (**Figure 1**), 3495 who received LR and 52 079 who received NS. eTable 3 in Supplement 1 shows characteristics of excluded patients who received both fluid types. The median (IQR) age of included patients was 30 (25-37) years, 85.1% had HbSS genotype, and 6.6% had acute chest syndrome present on admission (**Table 1**). The median (IQR) fluid volume received on hospital day 1 in patients who received LR and NS was 1 L (1-2) and 2 L (1-3) (SMD 0.46), respectively. The median percentage of patients who received LR on hospital day 1 across hospitals was 2.1% (IQR, 0.0%-5.9%; range, 0.0%-97.0%) (eFigure 2 in Supplement 1).

Outcomes

The unadjusted mean (SD) number of HFDs was 24.8 (4.5) in those who received LR and 24.7 (4.4) in those who received NS. Using TMLE, patients who received LR had more HFDs compared with those who received NS (marginal mean difference, 0.4; 95% CI, 0.1-0.6 days) (**Figure 2**). Patients who re-

Figure 1. Study Flow Diagram



LR indicates lactated Ringer; NS, normal saline.

ceived LR also had more HFDs than those who received NS in all 3 sensitivity analyses (eTables 4-6, eFigure 3, eFigure 4 in Supplement 1).

Patients who received LR had shorter hospital lengths of stay (marginal mean difference, −0.4; 95% CI, −0.7 to −0.1 days), more intravenous opioid-free days (marginal mean difference, 0.4; 95% CI, 0.1-0.6 days), and lower risk of 30-day hospital readmission (marginal risk difference, −5.8%; 95% CI, −9.8% to −1.8%) compared with those who received NS. There were no differences in organ support-free days (marginal mean difference, 0.1; 95% CI, −0.03 to 0.20 days), blood transfusion-free days (marginal mean difference, 0.1; 95% CI, −0.05 to 0.3 days), hospital mortality (marginal absolute risk difference, −0.2; 95% CI, −0.6 to 0.1) or intravenous diuretic use (marginal absolute risk difference, −1.2; 95% CI, −2.9 to 0.5) (Figure 2).

Heterogeneity of Treatment Effect

Associations between LR vs NS for HFDs were heterogenous depending on the volume of fluid received on hospital day 1 and possibly HbSS genotype (**Table 2**). Among patients who received less than 2 L of fluid (n = 24 316), there was no difference in LR vs NS (HFDs marginal mean difference, −0.02; 95% CI, −0.4 to 0.3 days), whereas among those who received 2 or more liters of fluid (n = 31 258), LR was superior to NS (HFDs marginal mean difference, 0.5; 95% CI, 0.2-0.8 days). In patients with HbSS genotype (n = 47 303), LR was superior to NS (HFD marginal mean difference, 0.4; 95% CI, 0.1-0.7 days), whereas there was no difference (HFDs marginal mean difference, −0.2; 95% CI, −0.8-0.4 days) among patients without HbSS genotype (n = 8271).

Discussion

We compared the effectiveness of LR vs NS resuscitation in patients hospitalized with SCD VOEs across US hospitals. Although the most patients received NS, we found that those who received LR had small but significant improvements in outcomes including HFDs and rates of readmission. In addition, we identified clinical characteristics (fluid volume and HbSS genotype) that modified associations between LR vs NS and outcomes. To detect a difference in HFDs comparable to that identified in our study, an RCT would require a sample size of more than 3500 participants (assuming mean [SD] HFDs of 24.7 [4.4] in the NS group, a treatment effect of 0.4 days, α of 0.05 and 80% power). To our knowledge, no prior RCT of patients with SCD has enrolled a study population even half as large as that needed to confirm our findings and there have been no prior RCTs evaluating fluid therapy during VOEs.[31] In the setting of limited current evidence and where a future RCT is likely infeasible, our results support the use of LR over NS for early fluid resuscitation in patients hospitalized with SCD VOEs.

This work should be considered in the context of previous studies. In an observational study[10] of children with SCD admitted to 20 pediatric emergency departments, use of normal saline fluid resuscitation was associated with smaller improvements in pain scores and higher rates of admission to the hospital compared with patients who received no fluid, LR, or half NS. Compared with these prior results that included a comparator group that consisted primarily of no treatment (increasing risks of indication bias[32]), our study compared 2 active treatments and provides more robust evidence that LR may be superior to NS in patients with VOEs. Several RCTs have compared balanced to unbalanced fluid in patients without SCD.[21] Unlike these RCTs that suggested modest improvements in kidney-related outcomes with balanced fluid but no differences in HFDs, we found LR was associated with modest improvements in HFDs but no difference in organ support (including kidney replacement therapy)-free days or intravenous diuretic use. Similar to patients without SCD,[33] the effectiveness of LR over NS was strongest in patients who received more fluid volume.

We hypothesize that these observed results could be unique to patients with SCD and are possibly related to detrimental effects of unbalanced fluid increasing erythrocyte sickling. For example, sickle erythrocytes exposed to NS have increased stiffness, transit time, and propensity to microchannel occlusion compared with exposure to fluid with other

Table 1. Characteristics of Patients Admitted for Vaso-Occlusive Episodes

Characteristic	No. (%)			
	Overall (N = 55 574)	LR (n = 3495)	NS (52 079)	SMD
Demographics				
Age, median (IQR), y	30 (25-37)	29 (24-36)	30 (25-37)	0.08
Sex				0.06
Female	30 396 (54.7)	NA[a]	NA[a]	
Male	25 153 (45.3)	NA[a]	NA[a]	
Unknown	25 (0.0)	NA[a]	NA[a]	
Race[b]				0.11
Asian	101 (0.2)	6 (0.2)	95 (0.2)	
Black	51 162 (92.1)	3304 (94.5)	47 858 (91.9)	
White	944 (1.7)	44 (1.3)	900 (1.7)	
Other	2853 (5.1)	120 (3.4)	2733 (5.2)	
Unknown	514 (0.9)	21 (0.6)	493 (0.9)	
Discharge year				0.99
2016	9029 (16.2)	108 (3.1)	8921 (17.1)	
2017	8771 (15.8)	111 (3.2)	8660 (16.6)	
2018	8781 (15.8)	248 (7.1)	8533 (16.4)	
2019	9043 (16.3)	481 (13.8)	8562 (16.4)	
2020	7601 (13.7)	659 (18.9)	6942 (13.3)	
2021	7187 (12.9)	967 (27.7)	6220 (11.9)	
2022	5162 (9.3)	921 (26.4)	4241 (8.1)	
Characteristics present on admission				
Angus organ dysfunctions				
Cardiac	590 (1.1)	28 (0.8)	562 (1.1)	0.03
Respiratory	1203 (2.2)	117 (3.3)	1086 (2.1)	0.08
Neurologic	255 (0.5)	21 (0.6)	234 (0.4)	0.02
Hematologic	1769 (3.2)	107 (3.1)	1662 (3.2)	0.007
Hepatic	64 (0.1)	6 (0.2)	58 (0.1)	0.02
Kidney	2919 (5.3)	158 (4.5)	2761 (5.3)	0.04
Angus sepsis criteria	1447 (2.6)	94 (2.7)	1353 (2.6)	0.006
Gagne comorbidity score, median (IQR)	3 (0-4)	3 (0-4)	3 (0-4)	0.07
Kidney failure	3169 (5.7)	147 (4.2)	3022 (5.8)	0.07
Congestive heart failure	4548 (8.2)	221 (6.3)	4327 (8.3)	0.08
Pulmonary circulation disorder	3717 (6.7)	256 (7.3)	3461 (6.6)	0.03
Hb-SS disease	47 303 (85.1)	2848 (81.5)	44 455 (85.4)	0.10
Acute chest syndrome	3689 (6.6)	247 (7.1)	3442 (6.6)	0.02
Care received on hospital day 1				
Major surgery	50 (0.1)	5 (0.1)	45 (0.1)	0.02
Admission to the ICU	693 (1.2)	49 (1.4)	644 (1.2)	0.01
Admission to the intermediate care unit	8058 (14.5)	251 (7.2)	7807 (15.0)	0.25
Invasive mechanical ventilation use	36 (0.1)	NA[a]	NA[a]	0.003
Noninvasive mechanical ventilation use	184 (0.3)	NA[a]	NA[a]	0.03
Hydroxyurea use	17 760 (32.0)	1204 (34.4)	16 556 (31.8)	0.06
Volume of fluid received, median (IQR), L[c]	2 (1-3)	1 (1-2)	2 (1-3)	0.45

Abbreviations: Hb-SS, hemoglobin SS; ICU, intensive care unit; LR, lactated Ringer; NS, normal saline.

[a] Number of patients masked to protect deidentified data.

[b] Race was categorized by Premier, Inc; including the category of "other" race.

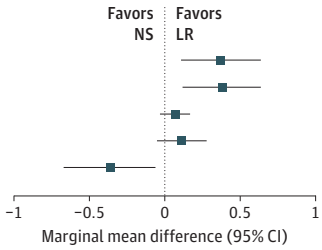
[c] Not included in models.

osmolarities.[8,34] These data suggest that NS may promote endothelial adhesion of circulating erythrocytes, known to play a role in the pathophysiology of vaso-occlusion. In addition, low serum pH in the setting of hyperchloremia-induced metabolic acidosis may promote erythrocyte sickling by decreasing hemoglobin oxygen affinity.[2,4,35] These factors may also support our finding of potential greater benefit of LR in the more highly hemolytic HbSS genotype. It is also possible that mechanisms in patients with SCD are similar to those proposed in patients without SCD (eg, minimization of hyperchloremia-induced acute kidney injury).[19] Future studies should seek to quantify the effect of intravenous fluid use on the degree of hemolysis between LR vs NS in humans with SCD and compare the effectiveness of balanced vs unbalanced fluid given for maintenance therapy (eg, half NS) that is frequently used after volume resuscitation.

Figure 2. Association Between Fluid Type and Outcomes in Patients With Vaso-Occlusive Episodes

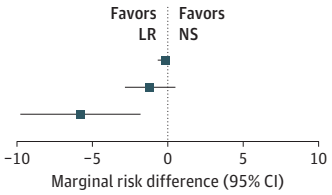
A Free day and length-of-stay outcomes

Outcome	LR, mean (SD)	NS, mean (SD)	Marginal mean difference (95% CI)
Hospital-free days (primary outcome)	24.8 (4.5)	24.7 (4.4)	0.37 (0.11 to 0.64)
Intravenous opioid-free days	25.1 (4.3)	24.9 (4.2)	0.38 (0.12 to 0.64)
Organ support-free days	29.9 (1.2)	29.9 (1.8)	0.07 (−0.03 to 0.17)
Blood transfusion-free days	29.9 (1.2)	29.9 (1.8)	0.11 (−0.05 to 0.28)
Hospital LOS in days[a]	5.2 (4.4)	5.2 (4.2)	−0.36 (−0.67 to −0.06)



B Dichotomous outcomes

Outcome, %	LR count, mean (SD)	NS count, mean (SD)	Marginal risk difference (95% CI)
Hospital mortality	4 (0.1)	169 (0.3)	−0.2 (−0.6 to 0.1)
Intravenous diuretic use	140 (4.0)	3309 (6.4)	−1.2 (−2.9 to 0.5)
30-d Readmission	1768 (50.6)	24 043 (46.2)	−5.8 (−9.8 to −1.8)



The columns LR mean (SD) and NS mean (SD) show unadjusted summary outcome measures for continuous outcomes. The columns LR count (%) and NS count (%) show unadjusted summary outcome measures for dichotomous outcomes. The marginal mean difference and marginal risk difference columns and the forest plots show the average treatment effect estimates yielded from the targeted maximum likelihood models. For free-day outcomes, positive effect estimates favor LR. For hospital LOS, negative effect estimates favor LR. For dichotomous outcomes, negative effect estimates favor LR. LOS indicates length of stay; LR, lactated Ringer; NS, normal saline.

[a]Negative hospital LOS marginal mean differences favor LR.

Table 2. Hospital-Free Day Heterogeneity of Treatment Effect for Lactated Ringer vs Normal Saline Among Patients With Sickle Cell Disease Admitted for Vaso-Occlusive Episodes

Hospital-free days by day 30	Mean (SD)		Marginal mean difference (95% CI)	*P* value for interaction
	LR	NS		
HbSS genotype				
No (n = 8271)	24.3 (5.2)	23.9 (5.2)	−0.2 (−0.8 to 0.4)	.07
Yes (n = 47 303)	24.9 (4.3)	24.9 (4.3)	0.4 (0.1 to 0.7)	
Admission location				
Hospital ward (n = 46 823)	24.8 (4.4)	24.8 (4.3)	0.4 (0.1 to 0.6)	.48
Intermediate or intensive care unit (n = 8751)	24.6 (4.7)	24.4 (4.9)	0.1 (−0.5 to 0.7)	
Fluid volume on hospital day 1				
<2 L (n = 24 316)	24.6 (4.6)	24.6 (4.6)	−0.02 (−0.4 to 0.3)	.03
≥2 L (n = 31 258)	25.2 (4.1)	24.8 (4.3)	0.5 (0.2 to 0.8)	
Kidney acute organ dysfunction present on admission				
No (n = 52 655)	24.9 (4.4)	24.8 (4.3)	0.4 (−0.4 to 0.3)	.40
Yes (n = 2919)	23.5 (6.1)	23.3 (6.1)	0.9 (−0.2 to 1.9)	

Abbreviation: HbSS, hemoglobin SS.

Strengths and Limitations

This study has both strengths and limitations. The large number of included patients facilitated precise estimates of relatively small effects. We are unaware of published reports of minimum clinically important differences (MCIDs) in patients with VOEs that could be used to inform whether the 1 half-day difference in HFDs between treatments is meaningful to patients. However, MCIDs for emergency department visits in patients without SCD may be as low as 1 hour[36] and, in the setting of high hospitalization and readmission rates for patients with SCD,[37] small differences in HFDs, length of stay, opioid use, and readmission may be highly relevant to patients, health care systems, and payers. Our results are subject to unmeasured confounding such as fluid administration in the emergency department,[38] time of day of fluid administration, and laboratory and vital sign measures. However, use of doubly robust TMLE rather than traditional methods (eg, propensity score matching) increases the likelihood that treatment effect estimates are valid in the setting of unmeasured confounding that affects only the treatment or outcome mechanism. The use of *ICD-10* codes to define HbSS genotype could be subject to misclassification. Patients with SCD are at in-

creased risk for congestive heart failure[39] and patients with SCD and volume overload have worse outcomes.[40] Thus, it is important to clarify that our results do not inform decisions about how much fluid to give during resuscitation, only the choice in fluid. In addition, because the volume status of included patients was unknown, it is possible that observed benefits could be due to lower harms from resuscitation with LR compared with NS in patients who are already euvolemic or hypervolemic. Although we defined exposure categories using charge codes for fluids commonly given for resuscitation, the administration rate and specific purpose of fluid administration (eg, bolus, maintenance) was not known. Although characteristics of excluded patients who received both fluid types were generally similar to those who received a single fluid type, it is possible that this exclusion criterion introduced selection bias. We did not quantify associations between fluid selection and potential devastating complications of SCD (eg, acute chest syndrome, thrombotic events); future studies should assess effects of fluid type on these outcomes.

Conclusions

Using a large, multicenter database to compare the effectiveness of LR vs NS resuscitation in patients hospitalized with SCD VOEs, we found that LR use was associated with small but significant improvements in several outcomes including HFD and hospital readmission. In addition, fluid volume and possibly HbSS genotype modified the effects of LR vs NS. Our results, in absence of prohibitively large RCTs that are unlikely to occur, support the use of LR over NS for patients admitted with SCD VOEs.

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Concept and design: All authors.
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