Lactated Ringers vs Normal Saline Resuscitation for Mild Acute Pancreatitis: A Randomized Trial

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Acute pancreatitis (AP) is a leading cause of hospitalization in the United States, resulting in significant morbidity and cost.[1] In the absence of proven pharmacologic interventions, early aggressive intravenous hydration has been the mainstay of treatment; however, although clinical practice guidelines and expert opinion agree on fluid volume, equipoise remains regarding optimal type.[1]

It appears that pH-balanced Lactated Ringer's (LR) solution is less likely to induce metabolic acidosis at large volumes compared with normal saline (NS) and results in supraphysiologic hyperchloremia, which may contribute to kidney injury.[2] Nevertheless, smaller trials comparing fluid type have yielded conflicting results.[3,4]

Methods

We performed a double-blinded randomized controlled trial to define the comparative efficacy of LR solution vs NS for AP resuscitation (Supplementary Materials). Patients presenting to the Los Angeles County Hospital with AP were randomized in a 1:1 ratio to receive intravenous hydration with LR vs NS. Patients in both groups received a 10 mL/kg bolus followed by continuous infusion at 3 mL/kg per hour. At 12 (±4), 24 (±4), 48 (±4), and 72 (±4) hours, subjects were evaluated by a blinded study physician.

The primary outcome of this study was change in systemic inflammatory response syndrome (SIRS) prevalence at 24 hours after randomization. Secondary outcomes included the change in SIRS prevalence at 48 hours and 72 hours, development of moderately severe/severe pancreatitis, requirement for intensive care unit admission, length of hospitalization, and adverse events.

Results

Among 331 patients who presented to the Emergency Department with AP between September 2018 and August 2019, 210 were excluded and 121 randomized to treatment with LR vs NS (Supplementary Figure 1). Baseline characteristics of the groups were similar, with most patients having mild pancreatitis (Supplementary Table 1). At enrollment, 17 (27.9%) patients in the LR arm and 14 (23.3%) in the NS arm had SIRS.

A last observation carried forward approach was necessary to analyze SIRS prevalence (Table 1) given that patients managed with LR were discharged earlier (ie, 44% in LR group discharged at 72 hours vs 28.3% of NS group). There was no difference in SIRS prevalence at 24 hours for LR vs NS, risk ratio (RR) 1.2 (95% CI 0.7–1.9) or at the 48- or 72-hour cutpoints (Table 1).

Intensive care unit admissions occurred less frequently in patients randomized to LR, 9.8% (6 of 61), compared with those receiving NS, 25% (15 of 60) (RR 0.4, 95% CI 0.2–0.9). These results remained consistent after adjusting for pancreatitis etiology, ethnicity, and baseline resuscitation (Table 1).

Median length of hospitalization was also shorter in the LR (3.5 days [interquartile range 2.0–5.9]) compared with the NS group (4.6 days [interquartile range 2.95–7.35]) ($P = .049$). Hyperchloremia developed less frequently at 24 hours in the LR group, RR 0.2 (0–0.6).

Local complications occurred in 6.6% (4 of 61) randomized to LR versus 15% (9 of 60) to NS (adjusted RR 0.3 [95% CI 0.1–1.5]). These included necrosis in 11 and fluid collections in 2. There was also a nonsignificant trend toward more frequent moderately severe/severe pancreatitis with NS, 25% (15 of 60) vs LR, 14.8% (9 of 61) (adjusted RR 0.5 [0.2–1.1]). There was no difference in organ failure or recurrent pancreatitis. One patient in the LR group who developed severe pancreatitis required laparotomy for abdominal compartment syndrome. There was no mortality. Per-protocol and intention-to-treat analyses yielded the same results. Adjustment pre-randomization fluid type and volume did not affect outcomes.

Discussion

Our aim was to clarify in a double-blind randomized controlled trial whether LR solution vs NS is the optimal fluid for acute pancreatitis resuscitation. Several small randomized controlled trials have yielded heterogeneous results.[3,4] Wu et al[3] demonstrated greater SIRS reduction at 24 hours in contrast to de-Madaria et al[4]; both groups

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Table 1. Outcomes in Patients With AP Treated With NS vs LR Solution

	NS (n = 60) n (%)	LR (n = 61) n (%)	RR	Adjusted RR[a]
ICU admission	15 (25)	6 (9.8)	0.4 (0.2–0.9)	0.3 (0.1–0.9)
Moderate-severe pancreatitis	15 (25.0)	9 (14.8)	0.8 (0.4–1.4)	0.5 (0.2–1.1)
Local complications	9 (15)	4 (6.6)	0.4 (0.1–1.3)	0.3 (0.1–1.5)
Organ failure	9 (15)	7 (11.5)	0.8 (0.3–1.9)	1 (0.4–2.7)
Adverse events	0	1	—	—
Recurrent AP post-discharge	8 (13.1)	6 (10.0)	1.3 (0.5–3.6)	0.9 (0.4–2.0)
Hyperchloremia (Serum Cl > 108 mm/L) at 24 h	15 (25.4)	3 (5.6)	0.2 (0–0.6)	0.2 (0.1–0.6)

	NS (n = 60) n (%)	LR (n = 61) n (%)	RR	Adjusted RR [b]
SIRS 24 h	19 (32.2%)	21 (37.5%)	1.2 (0.7–1.9)	1.1 (0.7–1.6)
SIRS 48 h	18 (38.3%)	18 (41.9%)	1.1 (0.7–1.8)	1.0 (0.6–1.5)
SIRS 72 h	14 (32.6%)	11 (32.4%)	1.0 (0.5–1.9)	1.0 (0.5–1.8)

	NS Median (IQR)	LR Median (IQR)	*P* value
Length of hospitalization (*d*)	4.6 (3–7.4)	3.5 (2–5.9)	.049
Fluid administered in first 24 h following randomization (*L*)	5.8 (4.8–6.8)	6.0 (5.2–6.9)	.194

ICU, intensive care unit; IQR, interquartile range.
[a]Adjusted for pancreatitis etiology, race/ethnicity, and baseline differences in outcome of interest (ie. local complications).
[b]Adjusted for baseline SIRS prevalence.

found that LR was associated with lower C-reactive protein levels suggesting an anti-inflammatory response. We anticipated a 50% baseline SIRS prevalence; however, observed initial SIRS prevalence was 26%. In addition, one-third of patients had a history of recurrent pancreatitis and repeat episodes are typically mild. These factors potentially reduced the power of the study, given that compensatory physiologic responses are more likely to be intact in mild pancreatitis; the impact of fluid type appears greatest in severe disease.[5] Patients in the LR group were also discharged earlier than the NS arm, making interpretation of SIRS prevalence at sequential time points challenging.

In addition, given that inadequate hydration correlates with adverse pancreatitis outcomes, large-volume resuscitation in both groups may have mitigated the influence of fluid type. The generalizability of our study is also limited in that patients at risk of fluid overload were excluded. We relied on physical examination to gauge volume status; inferior vena cava ultrasound would have provided more objective assessment. Although hyperchloremia was less frequent with LR resuscitation, pH measurements would have better defined the physiologic impact of fluid type.

Although we did not detect a difference in the prevalence of systemic inflammatory response syndrome, we demonstrated that LR decreased intensive care unit admission and shortened length of hospitalization. The effect was robust across pancreatitis etiologies and patient demographics. These findings have implications for health care costs and patient experience; however, require confirmatory studies specifically designed to address these endpoints.

One clue of the potential mechanism of this improvement was the trend toward less peri-pancreatic complications with LR. Experimental pancreatitis models suggest that reduction of extracellular pH favors zymogen activation and acinar injury.[6] This may be intensified at the level of the gland where the flow may be differentially reduced in the context of pancreatitis.[7] Thus, the protective effect of greater pH balance may be most pronounced for local inflammation. Lactate may also have a protective immunologic effect via its role in the regulation of Toll-like receptor–mediated inflammation.[8]

Although this trial did not show a difference in SIRS prevalence at 24 hours, LR appears to reduce the need for intensive care and shortens the length of hospitalization for AP. This provides the strongest evidence thus far to favor LR for the resuscitation of patients with AP. Studies enrolling the full range of pancreatitis severity are needed.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.10.044.

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Supplementary Methods

Patients

Patients were enrolled following approval by the University of Southern California Health Sciences Institutional Review Board. The trial was registered with clinicaltrials.gov (NCT03642769) before initiation. Written informed consent was provided before enrollment and randomization. All authors had access to the study data and approved the manuscript after review.

Patients presenting to the emergency department were eligible if they fulfilled 2 of 3 criteria: epigastric abdominal pain; serum amylase and/or lipase greater than 3 times the upper limit of normal; or imaging findings consistent with AP. Eligible patients were required to be evaluated and randomized by a study physician within 8 hours of diagnosis. A dedicated paging system in the emergency department was used to contact study personnel regarding potential participants and the clinical laboratory alerted the study team of every patient with an abnormal amylase or lipase result.

Exclusion criteria included severe pancreatitis as defined by the Revised Atlanta Classification, New York Heart Association Class $\geq$II heart failure, pulmonary edema, renal insufficiency (creatinine $>$1.9 mg/dL), and liver dysfunction (albumin $<$3 mg/dL or known cirrhosis). We also excluded patients with clinical signs of hypervolemia, including pulmonary congestion, peripheral swelling, and ascites, as well as those who were $<$18 years of age, pregnant, incarcerated, or unable to provide informed consent.

Intervention

Patients were randomized in a 1:1 ratio to receive intravenous hydration with either LR solution or NS. A computer-generated randomization sequence was provided by Southern California Clinical and Translational Science Institute. Allocation was concealed until time of randomization. Following randomization, another study physician blinded to fluid type was assigned to perform serial evaluations at 12 ($\pm$4), 24 ($\pm$4), 48 ($\pm$4), and 72 ($\pm$4) hours following the start of treatment fluid infusion. An opaque cover was placed over the treatment fluid bags to ensure double-blinding.

All patients regardless of randomization received their treatment fluid at the same weight-based rate algorithm; all patients received an initial 10 mL/kg bolus administered over 2 hours followed by continuous infusion at 3 mL/kg per hour. At 12 ($\pm$4) hours after randomization, subjects were examined by the blinded study physician and laboratory testing was obtained. If the patient's blood urea nitrogen (BUN) at 12 hours was not decreased compared with the value at randomization, patients received an additional 10 mL/kg bolus administered over 2 hours before resuming their infusion at 3 mL/kg per hour. Patients who did have a decrease in BUN at the 12-hour checkpoint continued their 3 mL/kg per hour infusion of the assigned fluid without an additional bolus. Beyond 24 hours, the fluid rate was managed at the discretion of the treating physician using the assigned fluid type.

At each checkpoint, the blinded study physician evaluated the patient for pain using the 1 to 10 Visual Analog Scale, diet type and tolerance, and signs of fluid overload, including pulmonary rales, jugular vein distension, peripheral edema, and ascites. The total amount of fluids and analgesics administered were recorded at each checkpoint. If participants were found to have developed signs of fluid overload, their treating physicians were notified and fluid rates were then deferred to their treating physicians, although it was requested that the patient continue their assigned fluid type. Any fluid administered before enrollment in the study was recorded.

Outcomes

The primary outcome of this study was the change in SIRS from the time of randomization to 24 hours afterward. SIRS was defined as fulfilling at least 2 of the 4 following criteria: (1) temperature $>38^{o}$C or $<36^{o}$C, (2) heart rate $>$90 beats per minute, (3) respiratory rate $>$20 breaths per minute or PaCO2 $<$32 mm Hg, (4) white blood cell count $<$4000 cells/mm^3 or $>$12,000 cells/mm^3 or $>$10% bands. Patients were considered to have SIRS at baseline if 2 of the 4 criteria were met at time of randomization.

Secondary outcomes included the change in SIRS prevalence from baseline to 48 hours and 72 hours, development of moderately severe or severe AP as defined by the Revised Atlanta Criteria, requirement for intensive care unit admission, length of hospitalization, and time to advancement to oral diet.

Statistical Analysis

From our prior observational pancreatitis cohort, we estimated a SIRS prevalence of 50% in patients managed with NS. Based on discussion with experts, we defined a clinically significant difference as a reduction in SIRS prevalence of 50% in LR relative to NS. This was in accord with prior small randomized trials on this topic.[3,4] According to a priori calculations, a sample size of 119 would allow us to demonstrate a clinically significant difference with a 2-sided alpha = 0.05 and a power of 80%. A total of 121 patients were ultimately enrolled because 2 patients were found to have a creatinine greater than 1.9 mg/dL, in violation of enrollment criteria, between the time of evaluation and bolus administration. The 2 patients were included in the primary intention-to-treat analysis but excluded from the per-protocol analysis.

Proportions were used to report categorical variables, means (standard deviation/confidence intervals) for continuous variables with normal distribution, and medians (interquartile ranges) for nonparametric distributions. Logistic regression was used to test the primary outcome of SIRS reduction at 24 hours, as well as categorical baseline variables and secondary outcomes including intensive care unit admission, adverse events, and changes in SIRS prevalence at 48 and 72 hours. Logistic regression was also used to adjust for baseline prevalence in the outcome of interest and for other potentially influential baseline factors, including the amount and type of fluid administered before enrollment, gender, race/ethnicity, pancreatitis etiology, comorbidities, baseline white blood cell count, hematocrit, and BUN. Unadjusted and adjusted odds ratios were converted to risk ratios using the method of Norton et al.[1]

For the continuous outcomes of days in the hospital and days to advance diet, we used the Wilcoxon Rank-Sum (Mann-Whitney) test and performed a stratified analysis to address pancreatitis etiology, race/ethnicity, fluid administration before enrollment, and transfers dictated by insurance plan or to alcohol rehabilitation facilities. Statistical analysis was performed using STATA 14.0 (College Station, TX).

Reference

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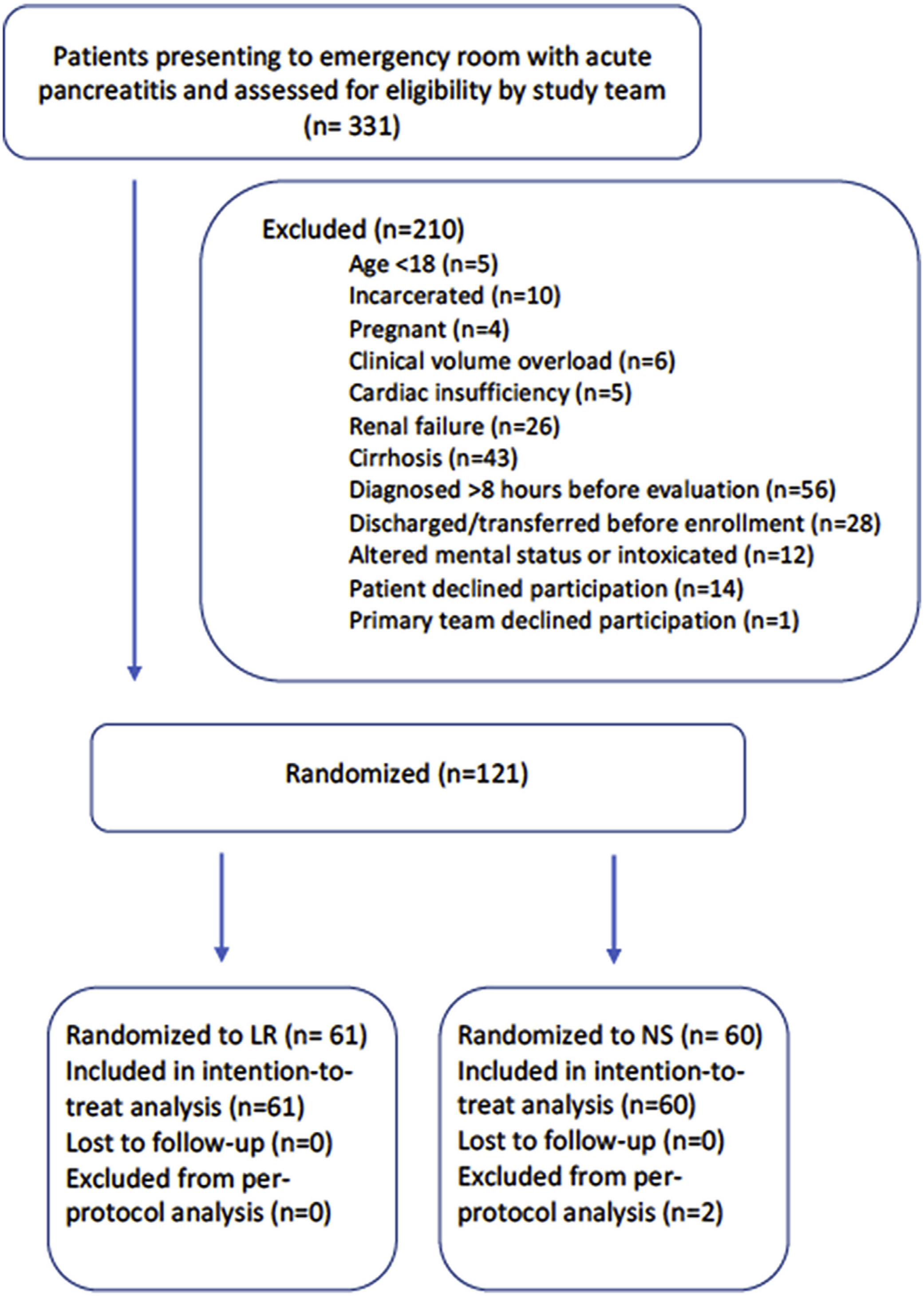

Supplementary Figure 1. Patient flow through the trial (CONSORT diagram).

Supplementary Table 1. Selected Baseline Characteristics

	NS (n = 60)	LR (n = 61)
	n (%)	n (%)
Male gender	33 (55)	30 (49.2)
Hispanic ethnicity	51 (85)	49 (80.3)
Gallstones	34 (56.7)	33 (54.1)
Alcohol	13 (21.7)	17 (27.9)
Triglycerides	5 (8.3)	3 (4.9)
Other	8 (13.3)	8 (13.1)
Comorbidities	31(50.8)	31 (51.7)
Diabetes mellitus	9 (15)	13 (21.3)
Hyperchloremia (Serum Cl >108 mm/L)	7 (11.7)	8 (13.1)
Prior pancreatitis	19 (31.2)	18 (30)
Fluid type before randomization		
NS only	35 (58.3)	37 (60.7)
LR only	2 (3.3)	5 (8.2)
Both NS and LR	18 (30)	13 (21.3)
None	5 (8.3)	6 (9.8)
Received different fluid before enrollment than assigned by randomization[a]	20 (33.3)	50 (82)
Mean (SD)		
Age	43.5 (14.2)	42.3 (14.0)
WBC	11.7 (6.8)	10.7 (4.5)
Hematocrit	40.3 (6.4)	39.1 (6.9)
Cr	0.9 (1.0)	0.7 (0.2)
BUN	13.7 (12.6)	11.3 (4.8)
Chloride	102.7 (5.8)	102.7 (7.5)
Median (IQR)		
Fluid volume before randomization	1.6L (1.0- 2.0)	2.0L (1.0–2.0)

BUN, blood urea nitrogen; Cr, creatinine; IQR, interquartile range; SD, standard deviation; WBC, white blood cell count.
[a]Significant ($P < .05$) difference in baseline category.