Fluid Choice Matters in Critically-ill Patients with Acute Pancreatitis: Lactated Ringer's vs. Isotonic Saline

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ABSTRACT

OBJECTIVES: To investigate the effect of different crystalloid solutions on clinical outcomes in critically-ill patients with acute pancreatitis (AP).

METHODS: We conducted a retrospective study of patients with AP admitted to the ICU using the Multi-parameter Intelligent Monitoring in Intensive Care III (MIMIC-III) database. We investigated the effect of fluid type; lactated ringer's (LR) vs. isotonic saline (IS) on hospital mortality rates, and ICU length of stay (LOS).

RESULTS: Hospital mortality of the 198 included patients was 12%. For fluid type, 32.9% were resuscitated with LR vs. 67.1% with IS. Hospital mortality was lower in the LR group (5.8%) vs. 14.9% for IS group, odds ratio of 3.10 [P=0.041]. This effect was still observed after adjusting for confounders. However, ICU LOS was longer in LR compared to IS group; 6.2±6.9 vs. 4.2±4.49 days respectively [P= 0.020].

CONCLUSION: The type of fluid used for resuscitation in AP may affect the outcome. LR may have survival benefit over IS in critically-ill patients with AP.

KEYWORDS: acute pancreatitis; Lactated Ringer's; Isotonic Saline; resuscitation; critically-ill

INTRODUCTION

Acute Pancreatitis (AP) remains one of the most common gastrointestinal disease processes[1]. Clinical practice guidelines put forth by the American College of Gastroenterology (ACG) regarding AP management emphasized large-volume fluid resuscitation for improved patient survival[2].

AP precipitates a systemic inflammatory process, which cascades into reduced end-organ perfusion, further inflammation, and subsequently, massive third-spacing of fluids[3]. Many indices of AP severity have been presented in order to guide the monitoring of hemodynamic status in those patients undergoing large-volume fluid resuscitation, especially within the first 48 hours of presentation[4]. ACG recommends Lactated Ringer's (LR) as the preferred isotonic fluid for resuscitation in acute pancreatitis over isotonic saline, (IS) based on expert opinion and supported by one randomized control study[5]. Wu et al demonstrated reduction in markers of systemic inflammation after comparable volumes of infusion with LR vs. IS, at 24 hours after presentation[6].

While the debate over LR vs. IS in improving outcomes remains indecisive, increased attention has been paid in recent years to the acid-base benefits of LR. Although both LR (pH 6.5) and IS (pH 5.5) have a lower pH than that of plasma, LR remains more physiologically complementary. IS infused in large volumes has shown marked non-anion gap metabolic acidosis and hyperchloremia in trauma patients[7, 8]. Saline- induced hyperchloremia was also associated with decreased renal blood flow, and worse clinical outcomes[9-11]. Also, the lactate component of LR is metabolized by the liver to reduce acidosis induced by acute fluid or renal losses. LR was found to be superior to IS in animal models of hemorrhagic shock . Use of IS for large-volume resuscitation in hemorrhagic shock increased the risk for metabolic acidosis, hyperkalemia, and vasodilation[12, 13]. We explored LR vs IS in critically-ill patients with acute pancreatitis and its effects on acid-base profile and outcomes.

METHODS

Study design

A retrospective study comparing the outcomes of critically-ill patients with acute pancreatitis based on the type of crystalloid fluid used for resuscitation in first 72 hours of their ICU stay.

Study Population

We used the Multi-parameter Intelligent Monitoring in Intensive Care (MIMIC-III) research data-base, developed by researchers from the Laboratory for Computational Physiology at Massachusetts Institute of Technology (MIT), Cambridge, MA, USA, and the Department of Medicine at the Beth Israel Deaconess Medical Center (BIDMC) Boston, MA, USA. The data-base has detailed information about intensive care unit patient stays, including high-resolution vital sign trends and waveforms, laboratory data, therapeutic interventions, discharge summaries, radiology reports and International Classification of Diseases, 9th Revision (ICD-9) codes for all patients admitted to BIDMC ICU between 2001 and 2012. Patients were de-identified in a Health Insurance Portability and Accountability Act-compliant manner. The institutional review boards of BIDMC and MIT approved the use of the MIMIC-III database[14, 15].

We included adult patients (> 18 years) admitted directly to the intensive care unit from the emergency department with acute pancreatitis. The diagnosis of acute pancreatitis was made based on the ICD-9 code, and confirmed by elevated serum amylase and/or lipase (> three times the upper limit of normal), and/or finding on CT abdomen consistent with AP. Patients who received colloids were excluded. Patients with missing data (demographics, clinical or fluid intake/output), or with alternative diagnoses other than AP on admission to the ICU were excluded.

Study variables

We included demographic information such as age, sex and race. Predictors of severity included Simplified Acute Physiology Score II (SAPS-II), and Bedside Index of Severity in AP (BISAP) scores on admission, using worst values in the 1st 24 hours. Chart notes were reviewed for etiology of pancreatitis when applicable. Amount and type of resuscitation fluid were extracted from the database. The amount of fluid was expressed as total amount in first 24, 48 and 72 hours of ICU stay. Based on type of fluid, patients were categorized into two groups; LR vs. IS. If a given patient received both LR and IS, they were assigned to the group of predominant fluid amount administered in 72 hours. Serial biochemical profile and vital signs were extracted for the first 72 hours. We specifically used serum bicarbonate and chloride as surrogates for non-gap metabolic acidosis. We reviewed serum levels of bicarbonate and chloride on admission and at 24 hours. The difference between the two points was calculated for both, and presented as percentage of change from the initial level (ΔHCO3% and ΔCl%).

Study outcomes

The primary study outcome was in-hospital mortality. The secondary outcomes were ICU length of stay, the trend of serum bicarbonate and chloride after 24hrs of resuscitation.

Statistical analysis

Age, SAPS score, vital signs, biochemical profile, amount of fluid and LOS were defined as continuous variables; race, gender, etiology of pancreatitis, BISAP score (as ≥3 or <3), type of fluid and hospital death were defined as categorical variables. Continuous variables are reported as mean with standard deviation or median with interquartile range when appropriate; categorical variables are reported as percentages. Comparisons between groups for categorical variables were evaluated using Pearson's chi-square test for contingency and for continuous variables a two-sided t test was used. To adjust for confounders, a multivariate analysis for in-hospital death was done using a logistic regression model. Variables were introduced into the model based on clinical and/or statistical significance (p value <0.1 on univariate analysis). In the event of co-linearity between variables, only one variable was included. The final model included the following variables: type of fluid, age, total amount of fluid in first 24 hours and BISAP score. As a supplemental analysis, we investigated the effect of LR. Vs. IS on changes in serum chloride and bicarbonate as surrogates for acidosis. All statistical tests and/or confidence intervals (CI), as appropriate, were performed at $\alpha = 0.05$. All reported P values were two sided rounded to three decimal places. Statistical analysis was performed using JMP Pro by SAS Institute.

RESULTS

Out of 1093 patients with ICD-9 of AP, only 198 satisfied inclusion and exclusion criteria; amongst excluded patients, 585 were transferred from another facility, 259 were initially admitted to the general medical wards or did not have AP on presentation, and 51 had missing data (**Figure 1**). The baseline characteristics are summarized in **Table 1**. LR group was older, received more fluid and had more patients with BISAP <3. Both groups had comparable SAPS-II scores. The overall mortality was 12.6%. Higher SAPS-II and BISAP scores on admission correlated with higher in-hospital mortality [P<0.0001]. The key results were summarized in **Table 2**. There was higher mortality in the IS group (16.1%) compared to the LR group (5.8%) in both univariate and multivariate logistic regression model; [P=0.029 and 0.045]

Table 1. Baseline Characteristics

	Lactated Ringer's (n=68)	Isotonic Saline (n=130)
Age, median (IQR), years	63 (52–74)*	56 (44–72)*
Men, %	51	50
Ethnicity, %		
Caucasian	78	76
African American	10	13
Other	12	11
Etiology, %		
Stones	36	21
Alcohol	14	21
Unknown	50	58
Amount of fluid, median (IQR), liters		
24 hours	7.2 (4.3–11.0)*	5.6 (3.5–7.9)*
48 hours	9.0 (5.3–15.8)*	7.5 (4.5–11.3)*
72 hours	10.3 (6.4–17.3)*	8.6 (4.7–14.0)*
BISAP ≥3, %	22*	35*
SAPS-II, median (IQR)	33 (24–41)	35 (25–47)

* P value < 0.05. Abbreviations: IQR, interquartile range; BISAP, Bedside Index of Severity in Acute Pancreatitis; SAPS-II, Simplified Acute Physiology Score-II.

Table 2. Results summary

	Lactated Ringer's (n=68)	Isotonic Saline (n=130)	P Value
In-hospital mortality, %	5.8	16.1	0.029
ICU LOS, mean (SD), days	6.2 (6.9)	4.2 (4.49)	0.020

Abbreviations: LOS, length of stay; SD, standard deviation

Figure 1. Cohort derivation and study scheme.

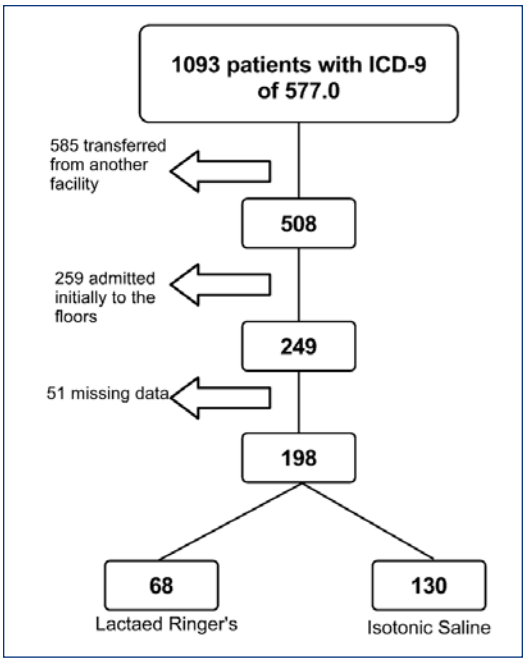


Figure 2. Mean change in serum bicharbonate after 24 hours of resuscitation.

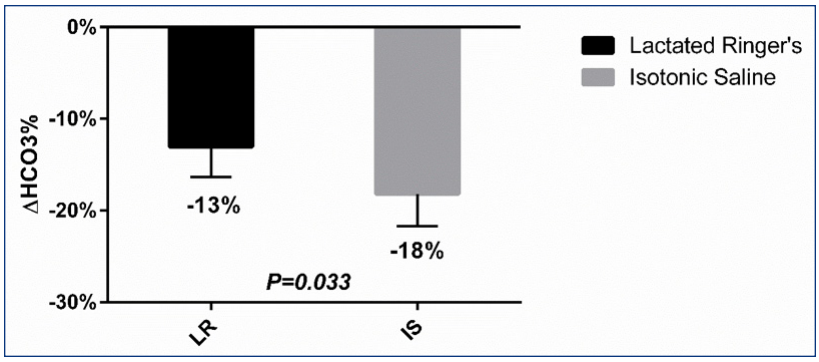
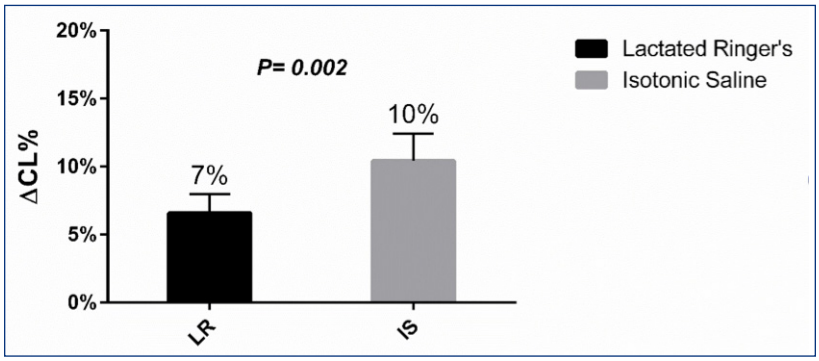


Figure 3. Mean change in serum chloride after 24 hours of resuscitation.



respectively with odds ratio of 3.10, 95% (CI 1.11-10.92). The multivariate model included age, amount of fluid in 72 hours and BISAP score to adjust for differences between the two groups. Interestingly, ICU LOS was longer in the LR compared to IS group; 6.2±6.9 vs. 4.2±4.49 days respectively, [*P*= 0.020]. Mean serum bicarbonate on admission was comparable between the two groups 22.16 vs. 20.84 mEq/L for LR and IS respectively, [*P*= 0.18]. More patients (44%) in IS group had a drop in serum bicarbonate after 24 hours of resuscitation compared to the LR group (36%); however, this didn't reach statistical significance [*P*= 0.323]. Among those whom HCO3 dropped, ΔHCO3% was more prominent in IS group -18% vs. -13% for LR, [*P*=0.033] (**Figure 2**). For chloride, although mean serum level on admission was higher in LR group 103.80 vs.100.17 mEq/L in IS group, [*P*=0.012], both groups had comparable percentage of patients who had increase in Cl levels after 24 hours 78% vs. 77% for LR and IS respectively [*P*=0.867]. Among those whom Cl increased, IS group showed higher ΔCl% of 10% vs. 7% for LR group [*P*= 0.002] (**Figure 3**).

DISCUSSION

In our study, we found that fluid choice in resuscitation of critically ill patients with AP may impact outcomes. Specifically, LR was associated with decreased mortality when used for resuscitation compared to IS. This association persisted after adjusting for differences between the two groups such as age, amount of fluid and severity on presentation. Moreover, we found that LR is associated with a less dramatic drop in serum bicarbonate and less increase in serum chloride; thus, reduced incidence of acidosis. Our study adds to the growing body of evidence suggesting that LR is more physiologically compatible with human serum than normal saline, and is associated with better outcomes in different settings, including AP.

The findings from our study, and previous studies are all consistent with the identified advantages of LR over IS in terms of reduction in SIRS, lower CRP level at 24 hours, improved pH-homeostasis, and electrolyte balance[13, 16-18]. We hypothesized that all of these advantages may culminate into a survival benefit. Moreover, a well-known phenomenon related to large volume saline infusion is the development of hyperchloremic metabolic acidosis[19], which further builds a case for the superiority of LR over IS in AP, and thus to the observed lower mortality with LR. This also supports our finding of a more prominent %ΔHCO3 drop (p=0.033) and %Δ Cl increase (p=0.002) in the IS group than LR after 24 hours of resuscitation. The above findings coincide with the fact that metabolic acidosis itself, is a part of the pathophysiology of AP[20]. Despite the advantages observed with the use of LR, it was interestingly associated with a longer duration of hospital stay. Differences in the age between the two groups could be contributing to the longer hospital stay observed in the LR group. Noteworthy however, is the fact that the LR group showed lower mortality in our study despite an overall more advanced age, making the dominance of LR over IS in AP even more consequential. The observational nature of our study is susceptible to bias and confounding. We adopted a very rigorous inclusion and exclusion criteria which makes the study susceptible to selection bias and impacting sample size as we excluded patients who were transferred from other facilities or who

were initially admitted to the floor, which was necessary since the first 24 hours in AP is the most crucial in treatment. Other confounding variables included the amounts of fluid administered during first 24, 48 and 72 hours was higher in LR group. However, both groups received amounts of fluid (7.2L for LR vs. 5.6L for NS) that were almost within the recommended range by the ACG guidelines (6-12L) in the first 24 hours, which is considered the most crucial period for adequate treatment[5]. IS has been shown to cause vasodilation, thus requiring increased volumes for resuscitation[12]. Decreased amount of IS was used in our study, leading to a question of under-resuscitation, yet a larger amount would have led to higher acidemia and mortality. Although our patients showed varied proportions of ≥3 BISAP score in both groups (22% in LR group and 35% in IS group) they displayed comparable median SAPS II scores (33 for LR vs. 35 for IS). Nonetheless, we included BISAP in the multivariate model to adjust for any possible confounding. Also a major limitation of our study was that most of our patients received both IS and LR which is hard to control for in retrospective studies. We assigned patients to the group based on the predominant amount which still can introduce some bias. Another limitation of our study was that it included only AP in critically-ill patients from a single center, which should caution us from generalizing the results to a larger population. Although we attempted to adjust for confounders and differences between the two groups by multivariate logistic regression model (specifically age, BISAP score and amount of fluid), residual confounding by unmeasured covariates may not have been completely eliminated. Moreover, our study included patients (2001–2012) that were treated before the updated guidelines for management of AP were presented in 2013, which could raise the question that there was no consensus on treatment protocols during that time.

In conclusion, we showed that LR may have a survival benefit over IS in critically-ill patients with AP. We encourage similar studies to be conducted, in the hopes that the seemingly endless debate regarding the optimal choice of isotonic fluid resuscitation can reach a conclusion.

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