Fluid Resuscitation with Lactated Ringer's Solution Versus Normal Saline in Acute Pancreatitis: A Systematic Review and Meta-Analysis of Randomized Trials

Running title: Lactated Ringer's Solution Versus Normal Saline

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Abstract

Objectives

We aimed to perform a systematic review and meta-analysis of randomized controlled trials to summarize the overall association between the choice of fluid (lactated Ringer's [LR] or normal saline [NS]) and clinical outcomes.

Methods

A systematic literature search was performed in electronic databases to identify eligible randomized controlled trials. Meta-analyses with the random-effects model were used to estimate the pooled odds ratio (OR) for outcomes of interest with the administration of LR relative to NS, at 95% confidence intervals (CIs).

Results

There was a significant reduction in the odds of ICU admission and development of local complications, respectively, with the administration of LR among hospitalized patients with acute pancreatitis relative to administration of NS (pooled OR, 0.33; 95% CI, 0.13–0.81 and pooled OR, 0.43; 95% CI, 0.21–0.89, respectively).

Conclusion

Our findings are able to assist clinicians in the navigation of the proper choice of fluid in patients with acute pancreatitis.

Keywords

Acute pancreatitis, fluid resuscitation, lactated Ringer's solution, normal saline

Introduction

Initial management of patients who present with acute pancreatitis is mainly supportive, with fluid resuscitation remains the mainstay strategy.[1] Indeed, fluid resuscitation in the initial stages of acute pancreatitis has been associated with risk reduction in morbidity and mortality, while hemoconcentration can lead to hypotension and necrotizing pancreatitis.[2-4] Fluid resuscitation is typically administered at a rate of 5 to 10 mL/kg per hour, which can be achieved with isotonic crystalloid solution (either normal saline or lactated Ringer's solution).[1]

There has been a debate whether fluid resuscitation with lactated Ringer's (LR) solution, compared with normal saline (NS), is associated with reduced morbidity. Proponents of LR for fluid resuscitation cited the presence of lactate which can inhibit the activation of nuclear factor κB, a transcription factor involved in the pathogenesis of inflammation in acute pancreatitis.[5] Whether such observation translates into clinical superiority remains to be determined. Therefore, we aimed to perform a systematic review and meta-analysis of randomized controlled trials to summarize the overall association between the choice of fluid and clinical outcomes in patients with acute pancreatitis.

Methods

Our analysis was conducted in agreement with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statements.[6] A systematic literature search with no language restriction was performed in electronic databases, including PubMed, Embase, MEDLINE, Google Scholar, and Cochrane Central Register of Controlled Trials to identify eligible studies, published up to May 2021. The search strategy was built based on the following keywords and MeSH terms: “saline”, “sodium chloride”, “ringer’s lactate”, “Hartmann's solution”, “lactated ringer’s”, “pancreatitis”, “randomised”, and “randomized”. In addition, the reference lists of relevant articles were also reviewed to search for additional studies. Two investigators independently performed the literature screening to identify eligible studies. Studies eligible for inclusion were randomized controlled trials comparing the clinical outcomes between the administration of LR and NS in hospitalized patients with acute pancreatitis. We excluded studies with observational design, single-arm trials, non-randomized trials, and studies that involved patients with post-endoscopic retrograde cholangiopancreatography pancreatitis.

The outcomes of interest were the occurrence of systemic inflammatory response syndrome (SIRS) at 24 hours, 48 hours, and 72 hours, as well as admission into intensive care unit (ICU) and development of local complications (e.g., necrotizing pancreatitis, fluid collection, etc.). Each trial was independently evaluated

by two investigators, who also extracted the study characteristics. Study characteristics extracted included the first author's surname, trial design, the country where the trial was performed, age of participants, the rate of fluid resuscitation, and outcomes of interest. Two investigators assessed the risk of bias of the trials included with Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2).[7] The disagreement between the two investigators related to the inclusion of studies, extraction of data, and quality appraisal of included studies was resolved through discussion with the third investigator. Meta-analyses with the random-effects model were used to estimate the pooled odds ratio (OR) for outcomes of interest with the administration of LR relative to NS, at 95% confidence intervals (CIs). We examined the heterogeneity between studies using the I2 statistics and the $\chi 2$ test, with significant heterogeneity at 50% and $P<0.10$, respectively. All analyses were performed using Meta XL, version 5.3 (EpiGear International, Queensland, Australia).

Results

Our systematic literature search retrieved 834 hits, of which 537 were unique (titles retrieved after removing duplications). After screening against inclusion and exclusion criteria, four randomized controlled trials[8-11] were included, with a total of 248 patients hospitalized with acute pancreatitis (122 patients were randomized to LR, and 126 patients were randomized to NS). The included randomized trials in the meta-analyses were from the United States[8,11] (n = 2), Spain[9], and Thailand[10]. Details of the included studies are shown in **Table 1**. The regimen of fluid resuscitation differed across the included trials; the trial by Wu et al[8] and Choosakul et al[10] administered 20 mL/kg of fluid bolus during a period of 30 minutes, followed by continuous infusion of 3.0 mL/kg/h; the trial by de-Madaria et al[9] administered 15 mL/kg of the study fluid in 60 minutes, followed by 1.2 mL/kg/hour of the study fluid for three days for patients with hypovolemia, but employed a different regimen for other patients; the trial by Lee et al[11] administered a 10 mL/kg fluid bolus followed by continuous infusion at 3 mL/kg per hour.

The meta-analyses revealed no statistically significant difference in the odds of development of SIRS at 24 hours and 48 hours, respectively, with the administration of LR among hospitalized patients with acute pancreatitis relative to administration of NS; the estimated effect though indicated risk reduction (**Fig. 1**; pooled OR, 0.60; 95% CI, 0.22–1.62; P = 0.13, n = 248 for development of SIRS at 24 hours; pooled OR, 0.70; 95% CI, 0.30–1.63; P = 0.27, n = 208 for development of SIRS at 48 hours), but is with inadequate evidence against the hypothesis of 'no significant difference' at the current sample size. Nevertheless, the meta-analyses revealed a statistically significant reduction in the odds of ICU admission and development of local complications, respectively, with the administration of LR among hospitalized patients with acute

pancreatitis relative to administration of NS (**Fig. 1**; pooled OR, 0.33; 95% CI, 0.13–0.81; P = 1.00, n = 201 for ICU admission; pooled OR, 0.43; 95% CI, 0.21–0.89; P = 0.83, n=248 for development of local complications)

Discussion

This is the first systematic review and meta-analysis to summarize the overall association between the choice of fluid and clinical outcomes in patients with acute pancreatitis from randomized controlled trials. Previous systematic reviews[12,13] considered observational evidence, with potential confounding and selection bias. Although there was no risk reduction in the occurrence of SIRS with LR, the findings where LR reduced the risk of ICU admission and the development of local complications indicate that the anti-inflammatory effects of LR could assume clinical benefits in patients with acute pancreatitis. In fact, the development of SIRS is merely a marker of poor outcomes, while preventing complications is the goal of therapy for patients with acute pancreatitis.[1]

Our analysis was limited by modest sample sizes and the absence of mortality outcomes due to inadequate studies for a pooled analysis. Nonetheless, our findings should be able to assist clinicians in the navigation of proper choice of fluid in patients with acute pancreatitis and should be incorporated in treatment guidelines to inform clinical practice.

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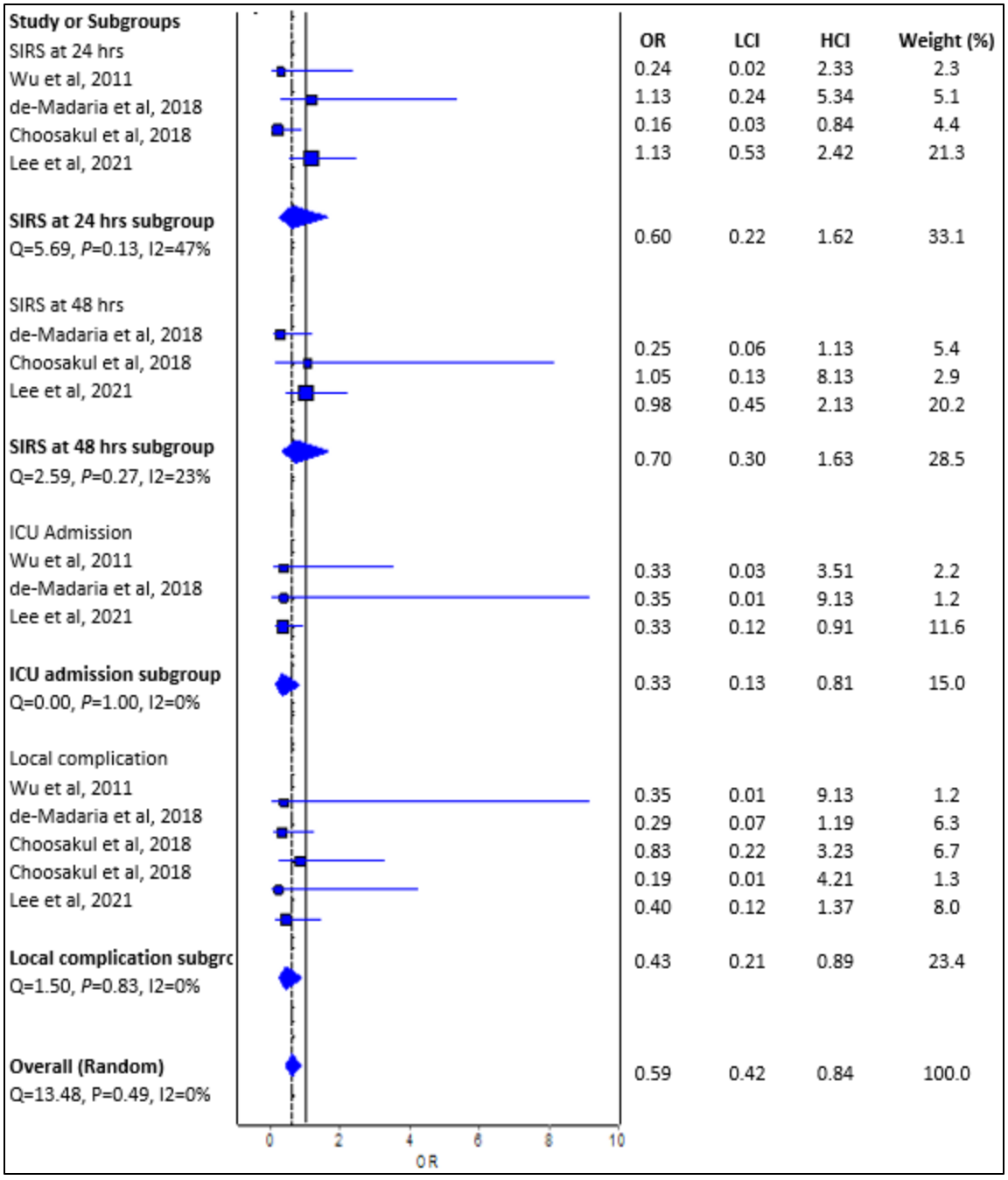

Figure 1: Pooled odds ratio of outcomes of interest with the administration of lactated Ringer's solution relative to normal saline in patients with acute pancreatitis

Table 1: Study Characteristics of Included Trials

Study	Study design	Country	Sample size	Age (median/mean; years)	SIRS at baseline (%)	SIRS at 24 hours		SIRS at 48 hours		ICU admission		Local complications		Risk of bias*
						LR n/N (%)	NS n/N (%)	LR n/N (%)	NS n/N (%)	LR n/N (%)	NS n/N (%)	LR n/N (%)	NS n/N (%)	
Wu et al, 2011[8]	Randomized, open label, 4-arm (2 × 2) factorial, parallel group, controlled pilot trial	United States	40	Median LR=50 NS=54	LR=50 NS=54	1/19 (5.3)	4/21 (19.0)	N/A	N/A	1/19 (5.3)	3/21 (14.3)	Pancreatic necrosis: 0/19 (0)	Pancreatic necrosis: 1/21 (4.8)	Some concerns
de-Madaria et al, 2018[9]	Randomized, triple-blind, controlled trial	Spain	40	Mean LR=63.8 NS=61.4	LR=47 NS=67	4/19 (21.1)	4/21 (19.0)	3/19 (15.8)	9/21 (42.9)	0/19 (0)	1/21 (4.8)	Pancreatic necrosis: 4/19 (21.1)	Pancreatic necrosis: 10/21 (47.6)	Some concerns
Choosakul et al, 2018[10]	Randomized, single-blind, controlled trial	Thailand	47	Mean LR=54.8 NS=48.3	LR=41 NS=35	2/23 (8.7)	9/24 (37.5)	2/23 (8.7)	2/24 (8.3)	N/A	N/A	Pancreatic necrosis: 0/23 (0) Fluid collection: 5/23 (21.7)	Pancreatic necrosis: 2/24 (8.3) Fluid collection: 6/24 (25.0)	Some concerns
Lee et al, 2021[11]	Randomized, double-blind, controlled trial	United States	121	Mean LR=42.3 NS=43.5	N/A	21/61 (34.4)	19/60 (31.7)	18/61 (29.5)	18/60 (30.0)	6/61 (9.8)	15/60 (25.0)	4/61 (6.6)	9/60 (15.0)	Low risk

ICU: intensive care unit; LR: lactated Ringer's solution; N/A: not available; NS: Normal saline solution; SIRS: Systemic Inflammatory Response Syndrome

*Risk of bias was assessed using Version 2 of the Cochrane risk-of-bias tool for randomized trials.