STUDY PROTOCOL

Saline vs. Lactated Ringers for Emergency Department IV Fluid Resuscitation

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A. Introduction

A.1. Health Problem Needing Intervention and Impact of Proposed Intervention

Administration of intravascular (IV) fluid is the most common emergency department (ED) procedure[1]. IV fluids are integral to increasing effective blood volume and ensuring organ perfusion in patients with volume depletion and dehydration[2]. There are many options of IV fluids providers can use when treating ED patients[3]. Surveys show physicians do not cite an evidence-based reason for selecting the crystalloid IV fluid used; the decision was likely to be influenced by type and location of practice[4,5]. A gap exists in the current literature, as there is no evidence for the optimal IV fluid choice for the ED patient requiring IV fluid before discharge.

Normal saline (NS) is commonly used as an IV fluid replacement in ED patients[6]. However, NS has been associated with increased risk of acidosis and acute kidney injury. This study will use a novel approach of a patient-centered outcome in a non-critically ill population to ascertain the optimal IV fluid for patient quality of recovery. The results of this study will inform provider's IV fluid decisions between NS and LR. More importantly, the results of this study will have the power to improve patient's quality of recovery following IV fluid administration and subsequent ED discharge.

B. Background

B.1. Prior Literature and Studies

Common IV fluids used for ED patients are normal saline (NS), a 0.9% sodium chloride solution, and lactated ringer's (LR), another isotonic saline solution[3]. There is a wealth of literature competing IV crystalloid solutions, like NS and LR, among others[7-9], yet administration of LR and NS by ED providers remains heterogeneous for non-critical ED patients.

NS has been shown to decrease renal arterial blood flow in healthy volunteers[10]. Large animal studies support the finding of increased metabolic acidosis and also cite hyperkalemia in subjects receiving NS, when compared to LR[11]. Increased risk of acidosis is most likely due to high chloride concentration[3,6]. LR is one of the "low-chloride" crystalloid solutions with a chloride load that is physiologic, or similar to the amount of chloride in human serum. While other low-chloride solutions have not been associated significantly different AKI or mortality than NS[12], observational studies have identified a protective association of LR for acute kidney injury and hospital mortality in critically-ill patients when compared to NS[13,14]. A recent meta-analysis found an association between high-chloride IV solutions, including NS, and inferior clinical outcomes[7], but no studies included an outcome of quality of recovery.

This study proposes comparing LR and NS in a non-critically ill population, ED patients receiving fluid before discharge. ED patients presenting with chief complaints likely to be associated with dehydration or volume depletion (nausea, vomiting or emesis, diarrhea, dehydration, heat stroke or exhaustion, and/or abdominal pain) will be included. One previous study has compared LR and NS in patients with severe diarrhea and was stopped for efficacy when LR corrected pH in subjects more quickly than NS[15].

This study will add to the current literature with a comparison of LR to NS on a patient-centered outcome for the most common procedure in emergency department patient populations.

B.2. Rationale for this Study

This is the first study to investigate the patient-centered outcome, quality of recovery, in a trial comparing LR and NS in an ED population stable for discharge. Previous studies indicate there could be an improved patient recovery when patients receive LR solution compared to NS solution as an IV fluid. Quality of recovery will be assessed by patient assessment of Comfort, Emotion, Physical Independence, Patient Support, and Pain.

Results from the proposed study could increase patient recovery at little or no increased cost. Normal saline and lactated ringer's solutions (1000 ml or CC) are similar costs (1.485 and 1.304 Payment Limits, respectively)[16], and both are readily available in most hospital formularies. This study proposes comparing two readily-available, low-cost IV fluids on the basis of patient-reported quality of recovery in patients discharged from the ED.

The study **hypothesis** is emergency department patients receiving lactated ringer′ s solution will have an improved Quality of Recovery when compared patients receiving normal saline.

C. Study Objectives

C.1. Primary Aim

The primary objective of this study is to compare the quality of recovery in ED patients receiving lactated ringer's and normal saline IV solutions at 24 hours after ED discharge.

C.2. Secondary Aim

The secondary aim of the study is to describe differences in healthcare utilization after ED discharge between subjects in the control NS and intervention LR groups.

D. Study Design

D.1. Overview & Design Summary

This is a single-blind, randomized controlled trial in a single Midwestern emergency department with 60,000 patient visits per year. Enrollment of 156 subjects is planned. Subjects will be randomized to receive a single administration of two liters of either normal saline or lactated ringer's solution. Evaluations will occur at baseline, one day following ED discharge, and seven days following ED discharge.

Potential participants will be screened upon ED registration. Subjects will participate in study for seven days (during ED visit with two remote follow-up contacts at one and seven days). Total duration of the study is expected to be 12 weeks.

D.2. Subject Selection

Subjects will be recruited in the emergency department by two trained research assistants (RAs). Subjects will be recruited beginning in May 2017.

D.2.a. Inclusion Criteria

Patients (1) with a chief complaint of: nausea, vomiting or emesis, diarrhea, abdominal pain, dizziness, weakness, heat stroke or heat exhaustion, dehydration, fatigue, or volume depletion; (2) are deemed by their ED provider to be clinically able to receive two liters of fluid; (3) are being administered fluids by their ED treatment team; and (4) are decided to be likely to be discharged from the ED are eligible for the study.

D.2.a. Exclusion Criteria

Patients without consistent access to a phone with text-messaging capabilities for the following seven days and/or without a primary care physician will be excluded from this study. Patients from the following groups will be excluded: pregnant, prisoners, did not speak English, were undergoing current chemotherapy, signs of jaundice, already received greater than 250 mL of IV fluids, or unable to provide informed consent.

D.2.b. Subject Recruitment Plans, Screening and Consent

Screening will begin as the patient checks in to the ED with the triage nurse and enters a chief complaint. Two RAs will monitor the emergency department electronic patient list in real time to identify patients with eligible chief complaints. The RA will approach the patient's provider to determine if patient meets inclusion criteria (2-4). If the provider determines the patient meets both inclusion criteria, the RA will approach the patient in his/her ED patient room to screen the patient for eligibility based on stated inclusion and exclusion criteria.

If patient meets all inclusion criteria and does not meet any exclusion criteria, the RA will discuss the study with the patient using a standard, IRB-approved script. If the patient is agreeable to participation in the study, written consent will be obtained and proof of research participation will be documented in the patient's electronic medical record.

D.2.c. Randomization Method and Blinding

Randomization of intervention will be 1:1 in randomized, permuted blocks. Randomization will be performed in SAS (SAS Institute), version 9.4. Blinded allocation ("Drug 1" or "Drug 2") will be placed in sealed opaque envelopes labelled by subject ID before the enrollment period begins. All research team members involved in patient enrollment and outcome assessment (survey administration) will not be involved in this randomization process.

D.3. Intervention

Following randomization, a RA will work with the nursing staff to procure the correct IV solution and administer the solution. Times of initiation and termination of fluid administration and amount of actual fluid administered will be recorded for covariate analysis.

D.3.a. Description

Both intervention and control medications will be delivered intravenously via peripheral venous access at room-temperature. Fluid administration rate will be 1,000 mL/15 minutes by pressure bag method and will be monitored by an RA.

Intervention is 2,000 mL lactated ringer's IV solution (see description below).

> "Each 100 mL of Lactated Ringer's Injection, USP contains sodium chloride 600 mg, sodium lactate, anhydrous 310 mg, potassium chloride 30 mg and calcium chloride, dihydrate 20 mg… A liter provides 9 calories (from lactate), sodium (Na+), 130 mEq, potassium (K+) 4 mEq, calcium (Ca++) 3 mEq, chloride (Cl−) 109 mEq and lactate [CH3CH(OH) COO−] 28 mEq. The electrolyte content is isotonic (273 mOsmol/liter, calc.) in relation to the extracellular fluid (approx. 280 mOsmol/liter). The pH of the solution is 6.6 (6.0 to 7.5)."[17]

Control is 2,000 mL of normal saline (0.9% sodium chloride).

D.3.b. Subject Compliance Monitoring

RAs will record time of initiation and completion of each bag of IV fluid and confirm patient is receiving correct fluid for allocation group. Any crossovers or premature stopping of fluid administration will be documented. Actual amount of fluid (mL) received will be documented.

D.3.c. Data Collection Procedures for Adverse Events

Any adverse event occurring in the ED would be recorded by the RA. Subjects will also be given contact information for a study physician, trained in emergency medicine, and will be instructed to call with concerns or to report any adverse events.

Further, an EM physician, not affiliated with the study, will be presented group data (blinded to treatment allocation) of 28-day patient medical treatment at the enrolling medical facility to assess safety for stopping. This chart review data will be collected by a research team member, blinded to subject group. Subject group ("A" or "B") will be added by study statistician (treatment ["LR" or "NS"] will not be revealed).

D.4. Study Outcome Measurements and Ascertainment

Outcomes will be recorded by trained RAs at time of ascertainment. RA obtaining outcome measurement will be blinded to subject allocation. Data will be entered and stored electronically on a secure server that can be accessed from any location at the enrolling site. Paper surveys will be saved in a locked file cabinet at the enrolling site.

At the time of enrollment, baseline characteristics of subjects will be collected by RAs by in-person interview (pre-intervention QoR-40 score) and from electronic medical record (age, gender). Some baseline characters will be collected at the chart abstraction (ED encounter disposition [discharged from ED/admitted to hospital/admitted to ICU], ED diagnosis type [by organ system]).

D.4.a. Primary Endpoint

The primary outcome of this study will be the post-treatment survey score of the Quality of Recovery-40 (QoR-40, see Attachment H-2) validated survey tool[18,19]. The survey has been used extensively in the surgery anesthesia literature to measure patient-

reported recovery across five independent domains: Comfort, Emotion, Physical Independence, Patient Support, and Pain. Survey scores range from 40 to 200.

RAs will administer the QoR-40 to subjects initially before any intervention is administered ("pre"). Twenty-four hours following discharge, the RAs will administer the survey again by telephone ("post"). During survey administration, RA will fill-out survey on paper, and it will later be entered into the electronic database. If patient does not answer, two additional phone calls will be made in the 24-48 hours following ED discharge. Time of "post" survey response will be recorded.

D.4.b. Secondary Endpoint

Secondary endpoints are designed to examine differences in healthcare administration between the NS control and LR intervention groups. Secondary endpoints will be assessed at two time points (1) at the 24-hour post-discharge phone call and (2) with a 7-day follow-up text message utilizing a two-way text messaging system.

The following secondary endpoints will be recorded:
(A) Sought additional healthcare for same complaint,
(B) Returned to an ED for same complaint,
(C) Filled an ED prescription from visit of enrollment, and
Each endpoint will be a dichotomous (yes/no) response. No adjudication of "same complaint" will be performed by the research team, as the intention is to capture the patient's interpretation of healthcare utilization from the illness.

D.4.c. Subgroups

No *a priori* subgroup analyses are planned. Any subgroup analyses performed will be solely for the purpose of hypothesis generation.

E. Statistical Plan

E.1. Sample Size Determination and Power

Sample size calculation was based on the detection of a 10-point difference on the QoR-40 survey scores. A 10-pt difference was selected as the minimum detectable difference maintaining clinical relevance, as supported by previous studies[18-21]. Sample size calculation ($\alpha = 0.05$, $\beta = 0.90$, 20% dropout, difference of 10 points) revealed a need for 156 total subjects.

E.2. Statistical Analysis

Baseline characteristics. Baseline characteristics will be reported with summary statistics as appropriate (mean, SD, median, IQR) and differences in characteristics will be conducted using t-test for continuous variables and chi-square test for categorical variables. If any baseline characteristics have significant differences, those behaviors will be reported in the results section and an adjusted analysis will be performed on primary and secondary variables to assess the impact of the imbalances.

Primary outcome. The primary outcome, pre-post difference in Quality of Recovery-40, will be analyzed using a t-test (if parametric) or Mann Whitney U Test (non-parametric) in an intention-to-treat (ITT) analysis. Due to the nature of emergency department

research, an additional analysis will be done by treatment received and compared to the primary ITT analysis.

Secondary outcome & safety analysis. Secondary outcomes will be reported as a relative risk with 95%CI in an ITT analysis. A safety analysis of selected secondary outcomes (return to ED and seeking additional healthcare for same complaint) will be performed by treatment received.

Covariate analysis. Differences in actual fluid administered and time from intervention to primary outcome will be assessed. If significant, analysis adjusting for covariates of time from intervention to primary outcome, post-QoR-40 administration, and amount of fluid (mL) received will performed with multivariable linear regression and multivariable logistic regression (primary and secondary outcomes, respectively).

F. Quality Control

F.1. Study Monitoring Plan

Study accrual will be reported weekly by RAs. Study accrual is expected to be about 13 subjects per week. Full research team meetings will occur if study accrual falls below 80% of expected total accrual for any end-of-the-week accrual reports. The purpose of the meeting will be develop and implement strategies to increase subject accrual. Potential solutions could include utilization of trained ED enrollers currently in the department, additional training and education of ED medical and nursing staff on the study, and recommendations to RAs by current clinicians on increasing visibility and awareness of the study during ED clinical shifts. Concerns will be addressed in a weekly meeting of RAs and investigators at enrollment site.

Safety reporting will occur after enrollment of every 30 subjects (the last group will be 36 subjects). If an adverse event is recorded, the Safety Coordinator will review the event within 24 hours. The local IRB will also be notified.

F.2. Data Review

Data from paper surveys and enrollment forms will be entered into a secure database by the RAs. At the end of enrollment and before analysis, one investigator will perform a 10% audit of the data. Concordance will be measured using a κ statistic. Following audit, the database will be locked for analysis.

G. Study Administration

G.1. Organization and Participating Centers

Enrollment for this single center study will occur at:

Emergency Treatment Center
Department of Emergency Medicine
University of Iowa Hospitals and Clinics
200 Hawkins Dr.
Iowa City, IA 52242

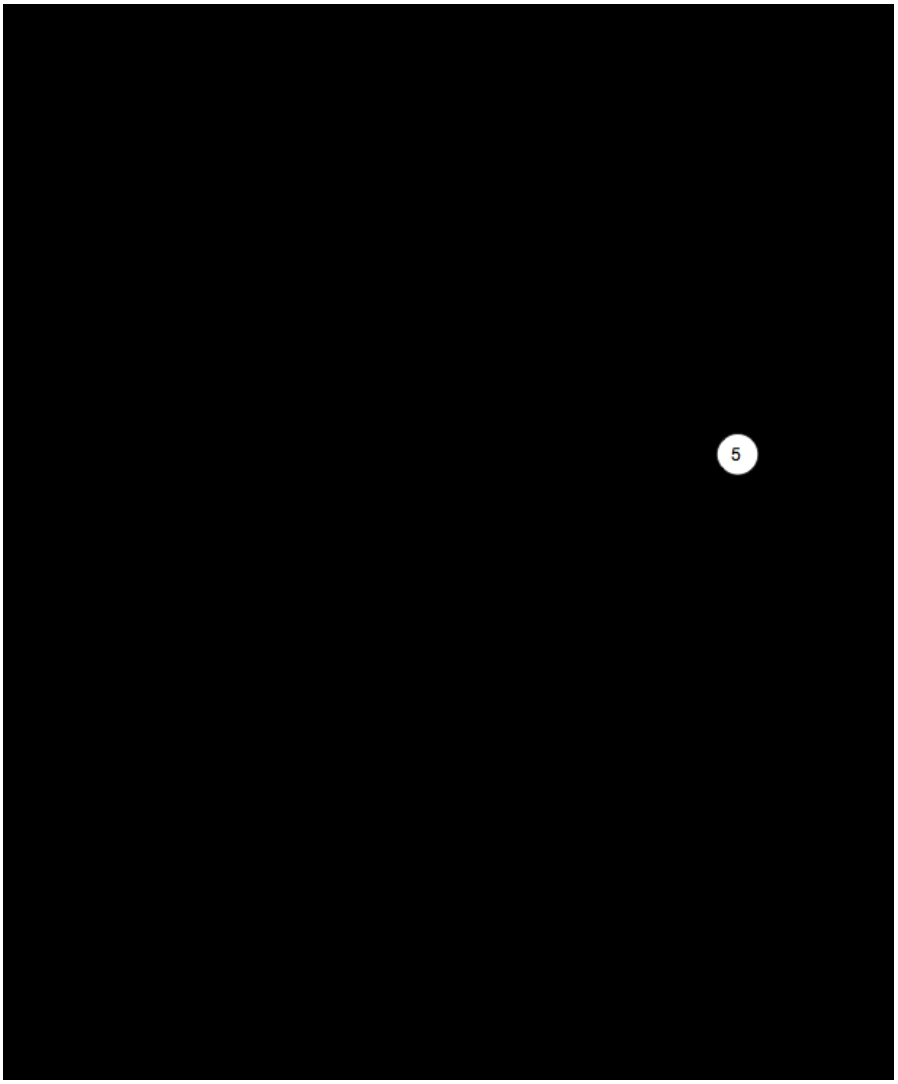
Investigators, study statistician, research assistants, and safety coordinator are affiliated with the University of Iowa.

H. Attachments

H.1. Procedure Table

	Timeline				
Measure	Baseline (Before Intervention)	During Intervention	Phone call: 24 hours after ED discharge	Text message: 7 days after ED discharge	Chart review: 28 days after ED discharge
Quality of Recovery-40	X		X		
Time and Amount of Fluid Administered		X			
Returned to ED for same complaint			X	X	
Sought additional healthcare for same complaint			X	X	
Filled ED prescription			X	X	
Adverse Event Monitoring		X	X	X	X

H.2. Primary Outcome Survey, "Quality of Recovery-40"[18]



I. References

1. Niska R, Bhuiya F, Xu J. National Hospital Ambulatory Medical Care Survey: 2007 emergency department summary. National health statistics reports 2010:1-31.
2. Grocott MP, Mythen MG, Gan TJ. Perioperative fluid management and clinical outcomes in adults. Anesth Analg 2005;100:1093-106.
3. Myburgh JA, Mythen MG. Resuscitation fluids. N Engl J Med 2013;369:1243-51.
4. Miletin MS, Stewart TE, Norton PG. Influences on physicians' choices of intravenous colloids. Intensive Care Med 2002;28:917-24.
5. Finfer S, Liu B, Taylor C, et al. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. Crit Care 2010;14:R185.
6. Barker ME. 0.9% saline induced hyperchloremic acidosis. J Trauma Nurs 2015;22:111-6.
7. Krajewski ML, Raghunathan K, Paluszkiewicz SM, Schermer CR, Shaw AD. Meta-analysis of high- versus low-chloride content in perioperative and critical care fluid resuscitation. Br J Surg 2015;102:24-36.
8. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 2013:CD000567.
9. Reddy S, Weinberg L, Young P. Crystalloid fluid therapy. Crit Care 2016;20:59.
10. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte(R) 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg 2012;256:18-24.
11. Martini WZ, Cortez DS, Dubick MA. Comparisons of normal saline and lactated Ringer's resuscitation on hemodynamics, metabolic responses, and coagulation in pigs after severe hemorrhagic shock. Scand J Trauma Resusc Emerg Med 2013;21:86.
12. Young P, Bailey M, Beasley R, et al. Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial. Jama 2015;314:1701-10.
13. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. Jama 2012;308:1566-72.
14. Zampieri FG, Ranzani OT, Azevedo LC, Martins ID, Kellum JA, Liborio AB. Lactated Ringer Is Associated With Reduced Mortality and Less Acute Kidney Injury in Critically Ill Patients: A Retrospective Cohort Analysis. Critical care medicine 2016;44:2163-70.
15. Cieza JA, Hinostroza J, Huapaya JA, Leon CP. Sodium chloride 0.9% versus Lactated Ringer in the management of severely dehydrated patients with choleriform diarrhoea. J Infect Dev Ctries 2013;7:528-32.
16. Payment Allowance Limits for Medicare Part B Drugs. 2016.
17. lactated ringer's (Sodium chloride, sodium lactate, potassium chloride, and calcium chloride) injection, solution. 2007.
18. Myles PS, Hunt JO, Nightingale CE, et al. Development and psychometric testing of a quality of recovery score after general anesthesia and surgery in adults. Anesth Analg 1999;88:83-90.
19. Gornall BF, Myles PS, Smith CL, et al. Measurement of quality of recovery using the QoR-40: a quantitative systematic review. Br J Anaesth 2013;111:161-9.

20. Asakura A, Mihara T, Goto T. The Effect of Preoperative Oral Carbohydrate or Oral Rehydration Solution on Postoperative Quality of Recovery: A Randomized, Controlled Clinical Trial. PLoS One 2015;10:e0133309.
21. Lee WK, Kim MS, Kang SW, Kim S, Lee JR. Type of anaesthesia and patient quality of recovery: a randomized trial comparing propofol-remifentanil total i.v. anaesthesia with desflurane anaesthesia. Br J Anaesth 2015;114:663-8.