Official Title: "Does Intravenous Lactated Ringer's Solution Raise Serum Lactate?"

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Introduction

Since "early goal-directed therapy," early recognition of septic shock using the serum lactate has become standard of care [1-4]. Indeed, the central place of lactate in sepsis care has been promoted by the Surviving Sepsis campaign, and it is now backed by financial incentives for hospitals with its adoption as a CMS Core Measure [5].

In this context, it is important to elucidate all possible causes of hyperlactatemia. Previous studies have shown that serum lactate increases in all shock states, not just septic shock [6]. Furthermore, lactate has also been shown to increase from albuterol [7], anti-retroviral medications, metformin, propofol, and alcohols [8].

According to Surviving Sepsis Guidelines, patients diagnosed with septic shock should receive 30 mL/kg of crystalloid solution within three hours [9]. One commonly used crystalloid, Lactated Ringer's solution (LR), contains 28 mmol/L of racemic lactate in the form of sodium lactate. While lactate is rapidly metabolized by the liver and kidney, aggressive fluid resuscitation with LR may transiently raise serum lactate, potentially confounding the interpretation of this test.

There has only been one trial looking at the question of whether administration of LR raises serum lactate. That study did not show a difference in lactate levels in those receiving LR versus those receiving alternative crystalloid solutions. However, that study used only 1 liter of LR delivered over one hour [10]. As mentioned above, patients in

47 septic shock are mandated to receive 30 mL/kg of crystalloid solution, and the fluids are
48 typically given at a rate faster than 1 liter per hour. Therefore, when LR is given at a
49 volume and rate more similar to what is done for septic shock patients, LR may have an
50 effect on serum lactate level that was not identified in the previous study.
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52 Thus, we propose a double-blind, randomized controlled trial to investigate whether the
53 administration of intravenous LR at 30 mL/kg increases levels of serum lactate. As our
54 study compares the effect of NS and LR, it lends itself easily to secondarily investigating
55 changes in sodium (Na), chloride (Cl), and pH in the NS group compared to the LR
56 group.
57
58 **Materials and Methods**
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60 **Study Design and Setting**
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62 This will be a double-blind, randomized controlled trial performed on a group of healthy
63 volunteers, made up primarily of family, friends, and colleagues of the investigators.
64
65 All subjects will be healthy volunteers aged 18 years or older. Healthy volunteers are
66 defined as subjects with no acute symptoms who meet none of the following exclusion
67 criteria: pregnant, breast-feeding, prisoners, history of conditions associated with fluid
68 overload (congestive heart, renal, or hepatic failure), baseline serum lactate level >2.2
69 mmol, and baseline creatinine >1.5 mg/dL.

All volunteers will fill out a short data collection form assessing their age, weight, gender, and medical history. All volunteers will signed a written consent, approved by the IRB.

A random-number generator will be used to assign each subject to either LR or NS. After assignment, a pharmacist with no role in data collection prepared the fluids in a locked room. The pharmacist will use an opaque black bag to obscure the fluids. The subjects will then receive 30 mL/kg rounded to the nearest 100 mL of the solution to which they were randomized.

An investigator will place an 18 gauge IV in one upper extremity, and an initial serum lactate and electrolyte panel will be drawn, measured using the i-STAT 1 analyzer (Abbott Point of Care, Princeton, NJ). Fluids will be administered as a rapid bolus via pressure bag. Post-treatment blood will be drawn from the contralateral upper extremity five minutes after the conclusion of the IV fluid administration.

Outcomes

The primary outcome will be the difference in change in serum lactate levels between the LR and NS groups. Secondarily, we will compare the change in lactate within each group (before and after treatment), and we will compare the change in pH, creatinine, bicarbonate, Na, and Cl levels between NS and LR groups.

Data Analysis

We powered the study as follows. A sample size of 30 achieves 80% power to detect a difference of 0.5 mmol/L in the mean change in lactate between the NS and LR groups assuming a standard deviation of differences of 0.5 and an alpha of 0.05. We chose the value of 0.5 mmol/L by clinical gestalt based on what we consider a clinically significant difference in lactate levels. Before and after treatment lactate levels will be compared within each group using paired t-tests. We will compare the change in mean lactate and the change in other variables (pH, creatinine, bicarbonate, Na, and Cl) between the LR and NS groups using two-tailed t-tests.

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