# Intravenous Fluids

## Which Recipe?

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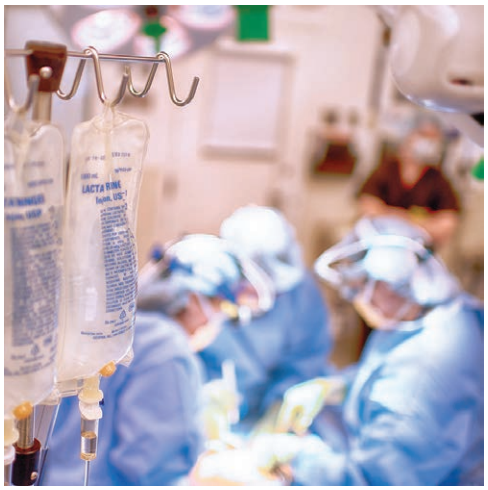
In this edition of Anesthesiology, Maheshwari *et al.*[1] report on the Saline or Lactated Ringer's (SOLAR) trial, conducted at the Cleveland Clinic in the United States. The researchers tested the hypothesis that among more than 8,000 patients undergoing elective colorectal and orthopedic surgery, a composite outcome of in-hospital mortality and major postoperative complications would be less common among those given lactated Ringer's solution than patients given normal saline during surgery. However, contrary to the hypothesis, the researchers found that there was no important difference in postoperative complications between the two fluid groups. Further, there was no important difference in acute kidney injury. The authors concluded: "Clinicians can reasonably use either fluid for routine vascular volume replacement in patients having noncardiac surgery." So, can we now safely give saline to all noncardiac surgical patients, particularly higher-risk patients? As often happens with clinical questions, the devil is in the detail.



**"…can we now safely give saline to all noncardiac surgical patients, particularly higher-risk patients?"**

When it comes to the question of which crystalloid, there has been debate over several decades as to whether it is clinically wise to use 0.9% saline, the simplest and cheapest fluid, and the favorite of many. An alternative view is that 0.9% saline, often derided as (ab)normal saline, is clinically inferior to more physiologic fluids, also known as balanced or buffered fluids. The most widely used of these more physiologic fluids are the lactate-containing fluids, such as lactated Ringer's and the very similar, but not identical, Hartmann's solution. Other alternatives are fluids with acetate anions including Ringer's Acetate and Plasmalyte. Many think the most important difference between these fluids and saline is the amount of chloride. Concerns about chloride in saline include hyperchloremic metabolic acidosis and kidney injury.[2–4]

The major strengths of the SOLAR study are that it is prospective and involves thousands of patients undergoing the most common major general surgical and orthopedic operations. SOLAR also has limitations. Although the researchers used an intensive multiple crossover approach for 2-week cluster allocation of fluids for all patients, SOLAR is not a randomized trial. A large, well-conducted, pragmatic, randomized trial provides evidence that is less likely to have confounders (biases) that may distort the results.[4] When interpreting SOLAR, we cannot be fully confident that known knowns, known unknowns, and unknown unknowns (thank you Donald Rumsfeld) are truly randomly allocated to minimize bias. To counter this concern the SOLAR authors conducted sensitivity analyses, suggesting an unrecognized confounding factor would need a substantial relative risk to affect the results. Nonetheless, this is evidence at a lower standard than a randomized trial. Further, the trial was unblinded, which may be a bigger risk for bias[4] than being nonrandomized. In part, this is because postoperative fluids were at the discretion of unblinded clinicians, as were decisions around levels of postoperative care.

Another important perioperative question is how much fluid? The SOLAR investigators note that the study was conducted when smaller volumes of perioperative fluids were in favor: SOLAR patients received an average of 1.9 l of fluid during surgery. This practice contrasts with the findings of the Liberal Fluid Therapy in Major Abdominal Surgery (RELIEF) study,[5] a large multicenter, randomized trial, that asked: How much fluid for major abdominal

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surgery? The RELIEF protocol called for Hartmann's and similar solutions with saline actively discouraged. Like SOLAR, there was no difference in the primary outcome in RELIEF. However, patients in the RELIEF liberal arm who received on average 3 l of intraoperative crystalloid had less acute kidney injury than those in the restrictive group who received 1.7 l. What would happen if SOLAR patients undergoing general surgery received 3 l of saline? Another important contrast between SOLAR and RELIEF is that the RELEIF fluid volume allocations were continued up to 24 h after surgery: The restrictive group received 3.5 l in the first 24 h, including surgery, and the liberal group about 6 l. SOLAR only accounts for fluids given in the operating room. What would be the effect of 6 l of saline over 24 h?

An earlier study that partly prompted the SOLAR hypothesis is the multicenter retrospective cohort study conducted by Shaw *et al.*,[6] who found fewer major complications among surgical patients who received Plasmalyte when compared with saline in U.S. hospitals. In discussing their results, the SOLAR investigators downgraded the conflicting results of the study by Shaw *et al.* because that study was nonrandomized, and instead preferred a Cochrane Review[4] of randomized trials of saline *versus* physiologic crystalloid fluids in adult surgical patients. Unfortunately, in the Cochrane Review the studies of mortality and renal replacement therapy had a combined sample size of fewer than 300 patients. For mortality analysis there were three trials with a total of 276 patients with six deaths in total, 2.9% in the saline group and 1.5% in the balanced group with wide confidence intervals, and therefore low-quality evidence. The Cochrane reviewers concluded: "Current evidence is insufficient to show effects of perioperative administration of buffered versus non-buffered crystalloid fluids on mortality and organ system function." The SOLAR investigators interpreted this to mean the reviewers concluded that fluid types did not differentially affect mortality or organ function and were consistent with their results. That may be overstating the case.

The SOLAR investigators are dismissive of metabolic acidosis with relatively small volumes of saline. However, among SOLAR patients the lowest mean pH was 7.36 in the Ringer's group and 7.32 in the saline group. Therefore many, if not all, patients in the saline group had hyperchloremic metabolic acidosis and many developed acidemia. The mechanism for this acidosis is easily understood using the Stewart approach: The relative difference between plasma sodium and chloride is decreased, producing a strong-ion acidosis.[3] A mild intraoperative hyperchloremic metabolic acidosis secondary to saline during elective surgery without large volumes is likely to be clinically unimportant because the acidemia itself is unlikely to affect organ function, and the acidosis is not a marker of underlying pathologic processes such as sepsis. However, as pH falls below 7.30, and particularly below pH 7.20, hydrogen ions increasingly disrupt protein structure and function in addition to any underlying pathologic causes of acidosis. So large volumes of saline will create acidemia that can be clinically important and aggravate lactate or other wide anion-gap acidosis. Added problems associated with saline-induced acidosis include increased acid–base testing and treatment and hyperkalemia. Even if one started with saline, fluid resuscitation may well be better with lower chloride fluids.

A concern about both the SOLAR study and the earlier study by Shaw *et al.*[6] regards using administrative data based on International Statistical Classification of Diseases and Related Health Problems (ICD) codes for research. Studies published in 2019 on surgical complications[7] and myocardial infarction[8] raise concerns about the accuracy of these administrative data. An editorial by Navar[9] referenced by the SOLAR investigators about the myocardial infarction study notes: "The present example is one of many that show how far we remain from being able to use EHR [electronic health record] data alone to conduct reliable, in-depth, and accurate observational research." Although errors in administrative data may be evenly allocated between groups, these concerns of possible bias undermine the reliability of point estimates of differences (number need to treat or harm) derived from administrative data particularly in nonrandomized unblinded studies.

SOLAR adds to the evidence that there may not be important added complications with limited volumes of saline for maintenance fluid therapy in the operating room during elective surgery. However, with risk of bias, notably postoperative fluid therapy and limited generalizability from a single U.S. center, SOLAR is not the definitive study to guide international practice. Would I now give saline to a typical patient in my anaesthesia practice: a 70-yr-old with hypertension, diabetes, mild chronic kidney disease for sigmoid colectomy, while planning more liberal fluid volumes? Based on current uncertainty, I would not use saline. However, considering the SOLAR findings, I have greater equipoise about these higher-risk patients participating in a large, pragmatic, blinded, multicenter, randomized trial of saline *versus* more physiologic fluids extending into the postoperative period, testing patient-centered outcomes such as longer-term mortality, hospital readmission, and quality of life.

## Competing Interests

The author declares no competing interests.

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