Selection of Intravenous Fluids

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Fluid resuscitation is one of the mainstays of shock management, and there has been tremendous interest in the choice of intravenous fluids. At present, isotonic crystalloid solutions are favored over colloid solutions. Among isotonic crystalloid solutions, 0.9% "normal" saline solution is perhaps the most widely prescribed medication in the United States. In clinical practice, the alternatives to 0.9% saline solution are balanced salt solutions that contain a physiologic amount of chloride and lactate or acetate as the base equivalent (Table 1). Two commonly used balanced salt solutions are Plasma-Lyte (Baxter) and Lactated Ringer's. Animal studies as far back as the 1980s[1,2] suggest that renal blood flow is reduced with the administration of chloride-rich crystalloid solutions compared with more physiologic solutions. A crossover trial in healthy humans[3] supports the animal findings, with decreased renal blood flow and cortical tissue perfusion after 0.9% saline solution administration. However, more recent studies[4,5] have been equivocal in demonstrating differential outcomes in using 0.9% saline solution versus balanced salt solutions.

Commentary on Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. N Engl J Med. 2018;378(9):829-839; and Self WH, Semler MW, Wanderer JP, et al. Balanced crystalloids versus saline in noncritically ill adults. N Engl J Med. 2018;378(9):819-828.

What Do These Important Studies Show?

In 2 pragmatic randomized clinical trials, Semler et al[6] (for the SMART [Isotonic Solutions and Major Adverse Renal Events Trial] Investigators) and Self et al[7] (for the SALT-ED [Saline Against Lactated Ringer's or Plasma-Lyte in the Emergency Department] Investigators) compared outcomes after 0.9% saline solution or balanced salt solution administration (Lactated Ringer's or Plasma-Lyte) in critically ill and non–critically ill populations, respectively. Given an anticipated small relative effect size, to be adequately powered, the SMART and SALT-ED trials needed to be large (SMART comprised 15,802 patients, and to our knowledge, is the largest clinical trial conducted in the intensive care unit [ICU] setting outside of cardiology and stroke).

SMART originally planned to enroll 8,000 patients during 60 unit-months to detect a 12% relative difference in the primary outcome of major adverse kidney events within 30 days (MAKE-30), with 90% power and $P < 0.05$ and assuming an incidence of MAKE-30 of 22% in the 0.9% saline solution arm. MAKE-30 is a composite end point composed of death, new initiation of renal replacement therapy (RRT), and persistent decreased kidney function (200% increase in creatinine level from baseline) at hospital discharge or 30 days. This end point is similar to what has been used in a number of large cardiology studies. At an interim analysis, the target study population was adjusted to 14,000 patients during 82 unit-months by the Data Safety Monitoring Board because observational data suggested that the incidence of MAKE-30 would be lower than anticipated ($\sim$15%).

Using historical data from the emergency department at Vanderbilt University, the SALT-ED trial planned to enroll 14,000 patients who received ≥500 mL of crystalloid solution in the emergency department over 16 months and would be hospitalized outside an ICU. The primary end point for the SALT-ED trial was hospital-free days to day 28, a composite of death and time out of the hospital for survivors, and this sample size provided 90% power to detect a 0.5-day difference in hospital-free days, $P < 0.05$.

There are several reasons that it would have been impractical to conduct these studies as conventional randomized clinical trials. First, the cost of performing such studies would have been prohibitive. Second, given the acute nature of the intervention, it would be impractical to obtain consent and randomly assign a patient before fluids were administered. Although there are alternative approaches that could be used to overcome this barrier (waiver of initial consent for research in an emergency setting, as is allowed by US Food and Drug Administration/Office of Human Research Protections provided very clear guidelines are met, or randomization after initial fluids were administered), these would each introduce additional complexities or potentially contaminate the intervention. Thus, both SMART and SALT-ED were embedded into clinical care at Vanderbilt University: after a pilot study demonstrated the feasibility of enrolling patients in the medical ICU and achieving separation of the 2 treatment arms,[4] the emergency department and ICUs were cluster randomized to alternating months in which balanced salt solutions (either Plasma-Lyte or Lactated Ringer's) or 0.9% saline solution were the default solutions recommended by the electronic health record unless the patient had relative contraindications or a physician chose to override the designated fluid. Possible contraindications for balanced crystalloids included hyperkalemia and brain injury (given concern for increased intracranial pressure risk from the relative hypotonicity of balanced crystalloid solution compared to 0.9% saline solution). Using this opt-out design, adherence was high. In SMART, of 13,085 orders for crystalloid solution during the balanced salt administration periods, the fluid allocation was overruled

Table 1. Properties of 0.9% Saline, Lactated Ringer's, and Plasma-Lyte Solutions

	0.9% Saline	Lactated Ringer's	Plasma-Lyte
Sodium, mEq/L	154	130	140
Potassium, mEq/L	0	4	5
Calcium, mEq/L	0	2.7	0
Magnesium, mEq/L	0	0	3
Chloride, mEq/L	154	109	98
Lactate, mEq/L	0	28	0
Acetate, mEq/L	0	0	27
Gluconate, mEq/L	0	0	23
Osmolarity, mOsm/L	308	273	294
pH	5.5	6.5	7.4

348 times for hyperkalemia, 278 for brain injury, and 232 per attending request (adherence of 93.4%). During the 0.9% saline solution months, 270 of 12,261 orders were overruled (adherence of 97.8%). In SALT-ED, adherence was 83.8% in the balanced crystalloid solution group and 92.8% in the 0.9% saline solution group.

Both studies demonstrated a reduction in MAKE-30 with the use of balanced salt solutions: 1.1% (14.3% vs 15.4%, $P = 0.04$) in SMART and 0.9% (4.7% vs 5.6%) in SALT-ED ($P = 0.01$). Subgroup analyses suggest that the difference in outcomes was greater among those who received larger volumes of fluids and those with sepsis (30-day in-hospital mortality 25.2% with balanced crystalloid solutions vs 29.4% with 0.9% saline solution, $P = 0.02$) within the critically ill population. Interestingly, however, the impact of the intervention on the subcomponents of MAKE-30 differed in the 2 trials. Although the major contributor to MAKE-30 in SMART was a difference in mortality, the major contributor for SALT-ED was the difference in those with persistent decreased kidney function (Table 2). Given the pragmatic nature of the study, a potential criticism of the MAKE-30 end point is that mortality, being initiated on RRT, and persistent decreased kidney function on discharge are outcomes with very different clinical significance for patients. Furthermore, baseline creatinine level had to be imputed for 10.7% of the study population in SMART and 35% of those in SALT-ED, which may heavily dictate the final subcomponent of MAKE-30. Data were also censored after hospital discharge, so the incidence of decreased kidney function at 30 days may have been overestimated, in particular in SALT-ED, for which the median number of hospital-free days to day 28 was 25, for a median hospital length of stay of 3 days. Ultimately, no difference in hospital-free days was identified in SALT-ED between the 2 groups.

How Do These Studies Compare With Prior Studies?

A number of observational studies[8,9] have suggested benefit with the administration of balanced salt solutions but are challenging to interpret because of the potential for residual confounding. In a sequential period study design, Yunos et al[9] examined the impact of balanced salt solutions and chloride-rich solutions for resuscitation; in this analysis, both colloid and crystalloid solutions were modified. During the balanced salt solution period, the incidence of acute kidney injury defined by the RIFLE criteria (risk, injury, failure, loss of kidney function, and end-stage kidney disease) and of RRT decreased significantly.

In contrast, the 0.9% Saline vs Plasma-Lyte 148 for ICU fluid Therapy (SPLIT) trial,[5] a double-blind cluster-randomized crossover trial of 0.9% saline solution versus Plasma-Lyte failed to show a difference in the rate of acute kidney injury (defined as RIFLE "injury" or "failure" between groups). In this analysis of 2,278 patients, the incidence of acute kidney injury was 9.6% versus 9.2% in those who received balanced salt solutions versus 0.9% saline solution (absolute difference, 0.4% [95% CI, −2.1% to 2.9]). The incidence of RRT was 3.3% versus 3.4% (absolute difference, −0.1% [95% CI, −1.6% to 1.4%]). Although not statistically significantly different, the incidence of death was lower with balanced salt solution administration, 7.6% versus 8.6% (absolute difference, −1.0% [95% CI, −3.3% to 1.2%]). This difference is similar in magnitude (∼1%) to that observed in SMART and raises the possibility that although very large in size for a critical care trial, the SPLIT trial was not sufficiently powered to observe small outcome differences. In addition, although the SPLIT trial was a blinded intervention, by the end of the study period, two-thirds of clinicians were able to correctly guess the treatment arm (likely due to the development of hyperchloremic metabolic acidosis in the 0.9% saline solution–treated patients), suggesting that there is a limited potential for blinding in such fluid trials.

Table 2. Selected Results of the SMART[6] and SALT-ED[7] Trials

Components of Primary Outcome	SMART (ICU)			SALT-ED (Non ICU)		
	Balanced Crystalloid, %	Saline, %	Difference	Balanced Crystalloid, %	Saline, %	Difference
In-hospital death before 30 d	10.3%	11.1%	0.8%	1.4%	1.5%	0.1%
New RRT	2.5%	2.9%	0.4%	0.3%	0.5%	0.2%
Final serum creatinine ≥ 200% of baseline	6.4%	6.6%	0.2%	3.8%	4.5%	0.8%
Major adverse kidney events within 30 d	14.3%	15.4%	1.1%	4.7%	5.6%	0.9%

Note: Percentages specify the percent of patients in the treatment group who experienced the stated outcome.
Abbreviations: ICU, intensive care unit; RRT, renal replacement therapy; SALT-ED, Saline Against Lactated Ringer's or Plasma-Lyte in the Emergency Department; SMART, Isotonic Solutions and Major Adverse Renal Events Trial.

What Are the Implications for Nephrologists?

SMART suggests potential benefit to the routine use of balanced crystalloid solutions in critically ill patients, especially those with sepsis. SALT-ED, although not positive for its primary end point of hospital-free days, demonstrated a lower incidence of MAKE-30 with balanced crystalloid solutions. Guidance on fluid management in non–critically ill patients is perhaps more limited because the intervention was applied only in the emergency department setting and did not span throughout the patients' entire non-ICU hospitalization. The pragmatic design of both studies allowed for rapid recruitment with limited contamination of the designated intervention and high adherence rate. Potential bias may have been introduced because hyperkalemia was listed as a relative contraindication for balanced crystalloids. However, 0.9% saline solution infusions may also be associated physiologically with hyperkalemia (because there can be movement of intracellular potassium into the extracellular space to maintain electroneutrality in the setting of hyperchloremic metabolic acidosis). This bias is evidenced by the decreased adherence observed in the balanced crystalloid solution arm of both studies. However, such deviations from allocation to balanced salt solutions could only diminish the observed difference in outcome between the 2 treatment arms. Based on the results of these studies, nephrologists are likely to see shifts in favor of balanced crystalloid solutions in fluid resuscitation. In clinical practice, the potential benefit of balanced crystalloid solutions must be weighed against the potential increase in cost. The current estimated cost of Plasma-Lyte and Lactated Ringer's is ~$4.50 compared to $2 per liter for 0.9% saline solution. The Plasma-lyte v Saline (PLUS) study,[10] an upcoming multicenter trial with 90-day mortality, is likely to further inform the ideal choice of resuscitation fluids for the critically ill. Similar trials in a multicenter setting are also needed in the emergency department and outside the ICU.

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