The origins of the “salt solution” for intravenous (IV) fluid resuscitation are attributed to the Scottish physician William O’Shaughnessy, who in 1831 recommended the use of a dilute salt solution to treat the profound hypovolemic shock of cholera. The first use in a patient followed shortly thereafter, when Thomas A. Latta administered a warmed IV solution of “two drachams of muriate, two scruples of carbonate of soda to sixty ounces of water” as salvage therapy to patients dying of cholera at the Leith Infirmary in Scotland. Thereafter, countless solutions of various compositions have been used across a wide range of clinical settings. Ironically, none are well aligned with the composition of the most omnipresent IV fluid used in medicine today, 0.9% (“normal”) saline solution. Although 0.9% saline solution has a similar sodium concentration to the aqueous phase of plasma (serum sodium concentration, 154 mmol/L), it has a higher relative chloride concentration and lower pH. Currently, there is little consensus on the ideal composition of IV fluid and the optimal rate and volume for administration. This has contributed in part to needless variation in practice and potential for iatrogenic harm. Recently, growing circumstantial evidence, mostly from observational studies, suggests there are significant dose/rate-dependent adverse effects associated with use of 0.9% saline solution for acute resuscitation attributed largely to the chloride load, including metabolic acidosis, hyperkalemia, acute kidney injury (AKI), and kidney replacement therapy. Although alternative “buffered” or balanced solutions that more closely align with plasma are widely available, no solution is considered predominantly cardiovascular (49%). Mean APACHE II (Acute Physiology and Chronic Health Evaluation II) scores were 14.1, two-thirds received mechanical ventilation, and mean baseline and admission serum creatinine (Scr) values were 0.98 to 0.99 and 1.15 to 1.18 mg/dL, respectively. Prior to enrollment, two-thirds had received a median volume of 1,000 to 1,200 mL of Plasma-Lyte 148 (PL-148; Baxter), while the remaining one-third received a median volume of 0 mL of 0.9% saline solution. The cumulative dose of study fluid given was small and similar between those allocated to 0.9% saline solution (median, 2,000 [interquartile range (IQR), 1,000-3,500] mL) and PL-148 (2,000 [IQR, 1,000-3,250] mL), with more than half being given in the first day.

AKI occurred in 9.2% and 9.6% in those receiving 0.9% saline solution and PL-148 (P = 0.77), respectively. No data described the timing of AKI relative to study fluid exposure. Despite blinding, 66% of treating clinicians (n = 36/55) correctly guessed the fluid type being administered. Kidney replacement therapy was used infrequently and was not different between groups (3.3% for PL-148 and 3.4% for 0.9% saline solution; P = 0.91). There was no significant heterogeneity of treatment effect by study fluid across prespecified subgroups or differences in any secondary end point. However, there was evidence of interaction between incidence of AKI and study site. This was likely either due to chance or

WHAT DOES THIS IMPORTANT STUDY SHOW?

The SPLIT trial used a novel, double-blind, cluster-randomized, crossover design. All patients admitted to 1 of 4 academic intensive care units (ICUs) in New Zealand between April and October 2014 who received crystalloid fluid therapy, not necessarily for acute resuscitation, were eligible.

Randomization occurred at the level of the ICU. Each ICU was allocated to 4 alternating 7-week blocks of study fluids, such that each ICU crossed over to provide each fluid type twice. Frequency, dose, and rate of fluid prescription were at the discretion of the treating clinician. The primary end point was incidence of AKI. Box 1 details the secondary and a priori planned subgroup analyses. Participation mean age was 60 years; two-thirds were men, the burden of comorbid conditions was low (no description of chronic kidney disease [CKD]), and most were admitted following elective surgery (57%), specifically cardiovascular (49%). Mean APACHE II (Acute Physiology and Chronic Health Evaluation II) scores were 14.1, two-thirds received mechanical ventilation, and mean baseline and admission serum creatinine (Scr) values were 0.98 to 0.99 and 1.15 to 1.18 mg/dL, respectively. Prior to enrollment, two-thirds had received a median volume of 1,000 to 1,200 mL of Plasma-Lyte 148 (PL-148; Baxter), while the remaining one-third received a median volume of 0 mL of 0.9% saline solution. The cumulative dose of study fluid given was small and similar between those allocated to 0.9% saline solution (median, 2,000 [interquartile range (IQR), 1,000-3,500] mL) and PL-148 (2,000 [IQR, 1,000-3,250] mL), with more than half being given in the first day.

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In the Literature

0.9% Saline or Balanced Crystalloid Fluids for Critically Ill Patients: SPLIT Decision?


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attributable to variability in population baseline and ICU-specific risks for AKI, though no further details were provided.

The findings of the SPLIT trial are certainly strengthened by its robust design, protocol adherence, and transparent reporting. However, SPLIT has limitations. First, SPLIT was a feasibility study intended to interrogate a novel cluster crossover design. Second, SPLIT did not have an a priori sample size estimation, such that when the size of the cohort is considered in the context of the low event rate for AKI, it is clearly inadequately powered to detect relatively small but potentially important differences in toxicity risk between fluid types. Third, average APACHE II scores were low, most patients were postoperative, and use of kidney replacement therapy was uncommon. These observations imply that the study cohort was not enriched with patients at increased risk for adverse kidney outcomes. Similarly, the prevalence of CKD and heterogeneity in treatment effect in this subgroup was not explored. Fourth, SPLIT used a surrogate measure as a primary end point, and the timing and frequency of Scr measurements were not standardized. A total of 6.5% had no Scr measured in the ICU. This likely occurred among those with low perceived risk for AKI, whereas in those at higher risk, more frequent measurements were likely performed. This would put SPLIT at risk for misclassification and ascertainment bias despite sensitivity analyses exploring extreme case scenarios in missing data. Similarly, if the toxicity of 0.9% saline solution is believed to be attributed to the chloride load given to patients, data for serum chloride concentration would further support biological plausibility; however, these data were not reported. Finally, fluid exposure occurring prior to enrollment (predominantly PL-148), the small total dose of study fluid given over a longer period, and the lack of standardized administration all likely dilute the capacity for SPLIT to detect any signal of harm or benefit associated with use of 0.9% saline solution or PL-148.

HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES?

Recently, several mostly observational studies have described fewer complications and improved outcomes among patients exposed to IV fluids with lower chloride concentrations. These data are consistent with experimental and small clinical studies of humans and the biological plausibility that 0.9% saline solution is not physiologic due to the high chloride concentration and lower relative strong ion difference compared to plasma. Accordingly, rapid and/or large volume administration, as in acute resuscitation, can directly incite an iatrogenic hyperchloremic metabolic acidosis. This acidosis may theoretically be exaggerated among susceptible patients, such as those with CKD, due to diminished capacity to handle and excrete chloride.

The use of balanced crystalloids in diabetic ketoacidosis, despite the concern that the added potassium content (potassium concentration, 5.0 mmol/L in PL-148) may exacerbate hyperkalemia, was found in a small randomized trial to be associated with greater increment in base deficit and lower serum chloride concentration compared to 0.9% saline solution. In a small randomized trial of intraoperative 0.9% saline solution compared to PL-148, 0.9% saline solution contributed to greater postoperative metabolic acidosis. In an observational study of adults undergoing major open abdominal surgery, the use of 0.9% saline solution compared to PL-148 was associated with greater electrolyte disturbances, more blood transfusions and acidosis investigations, and higher rates of complications, including receiving acute kidney replacement therapy.

The SPLIT trial adds to our body of knowledge on this issue. SPLIT is the first large-scale pragmatic comparative effectiveness evaluation of crystalloid fluid composition in ICU patients. However, SPLIT did not evaluate fluids in the same context as many of these aforementioned studies, in which the fluid doses given were larger and over shorter periods. Moreover, SPLIT did not specifically evaluate for a
dose-response association between fluid type and hazard of adverse outcome. As an example, a recent observational study of 0.9% saline solution use, compared to balanced crystalloids, was associated with higher risk for in-hospital death. However, there was no significant difference in AKI or kidney replacement therapy use in this large cohort of nonsurgical patients with sepsis.20

Thus, while the ideal electrolyte solution for IV fluid therapy in acute resuscitation is undiscovered, and may never be, SPLIT along with accumulated data clearly reinforce the importance of baseline risk and context when considering the potential hazard associated with IV fluids.

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

The SPLIT trial was a feasibility and comparative effectiveness trial, primarily aimed at detecting whether there was clinically important toxicity and/or harm associated with 0.9% saline solution when compared to PL-148. The key inferences from SPLIT could be either: (1) given it was a feasibility trial and woefully underpowered, it should be quickly scaled to provide more robust data suitable to inform clinical practice; or (2) among low-acuity predominantly postoperative ICU patients at relatively low risk for AKI, a small total dose of 0.9% saline solution compared to PL-148 (~2,000 mL), given over an extended period (about 1-3 days), does not appear to provoke an increased hazard for AKI. An alternative perspective of these findings would suggest that the relatively healthy patients enrolled in SPLIT, who received a small dose of fluid, were more than able to accommodate the hazard of 0.9% saline solution compared to PL-148 (if truly present), whereas in an enriched high-risk cohort, this may not have occurred.21 This is analogous to the hazard of AKI, kidney replacement therapy, and death associated with use of hydroxyethyl starch among ICU patients that appeared to be modified by case-mix and illness severity.22,23

Importantly, although these data are reassuring for lower risk patients receiving a little fluid, they do not provide clarity of the comparative effectiveness of these fluids for patients with greater baseline susceptibility to their toxic effects (ie, CKD) or those who may receive significantly more rapid and larger amounts. The SPLIT investigators acknowledge this and rightfully conclude by stating that additional high-quality trials are needed.12 Future clinical trials should also integrate a careful evaluation of the impact of the dose-response hazard associated with IV fluids on outcomes.21

The SPLIT trial should remind all clinicians to be respectful to the potential iatrogenic harm, both qualitative and quantitative, associated with fluid therapy. Similar to any drug used in acutely ill hospitalized patients, the prescription of IV fluid therapy should be context specific, with the dose, rate, and end points for administration clearly specified, such that it is given to the right patient, at the right time, and in the right context.

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ACKNOWLEDGEMENTS

Support: Dr Bagshaw is supported by a Canada Research Chair in Critical Care Nephrology.
Financial Disclosure: Dr Bagshaw has received research support from and consulted for Baxter. Dr Galm declares that he has no relevant financial interests.
Peer Review: Evaluated by the Deputy Editor and the Editor-in-Chief.

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