Time to Get SMART About SALT in the ED?

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Intravenous fluid resuscitation with crystalloids is one of the most common interventions performed in the emergency department and intensive care unit (ICU).[1] Normal saline (NS) and balanced crystalloids (BC) are often used interchangeably for this purpose, with considerable variation depending on physician preference and practice location. NS, the most widely used resuscitation fluid globally,[2] contains 154mmol/L of both sodium and chloride, and is isotonic to extracellular fluid. However, the high chloride concentration of NS has been shown to induce hyperchloremic metabolic acidosis.[1] In BC solutions other ions, such as lactate or bicarbonate, replace a proportion of the chloride found in NS, resulting in a more physiologic chloride concentration.[1] In 2015, the 0.9% Saline vs Plasma-Lyte 148 (PL-148) for ICU fluid Therapy (SPLIT) trial was published showing no difference in the rate of acute kidney injury in 2278 patients admitted to four ICUs in New Zealand who received either NS or BC3. This trial was not powered to detect small differences in mortality and did not control for the type of fluids received prior to arriving in the ICU. Given the ubiquity of fluid resuscitation and the potential for small differences in mortality to affect large numbers of patients, more evidence was required before declaring NS and BC equivalent or interchangeable. This article will review two recently published randomized controlled trials that compared NS to BC, and will consider how these and other ongoing trials may affect resuscitation fluid choices in the future.

The Saline Against Lactated Ringer's or Plasma-Lyte in the Emergency Department (SALT-ED) trial compared NS with BC solutions in a prospective sample of adults treated with IV fluids in the emergency department and subsequently admitted to the hospital outside of the ICU.[4] The BC arm included both lactated Ringer's and Plasma-Lyte, two commonly used BC solutions. To be eligible, patients had to receive at least 500ml of fluid in the ED and be admitted to the hospital outside the ICU. 6708 patients were randomized to receive BC and 6639 to receive NS. The median volume of crystalloid received was 1079ml, and 88.3% of patients received their assigned fluids exclusively. The primary outcome was Hospital-Free Days, defined as the number of days alive and out of hospital between their initial presentation to the ED and the end of follow up after 28 days. Secondary outcomes included the number of major adverse kidney events at 30 days (MAKE30), a composite outcome composed of death in hospital, new renal replacement therapy or a doubling in measured creatinine. Ultimately, there was no difference in hospital free days, but the group receiving BC had significantly lower rates of MAKE30 outcomes, with a number needed to treat (NNT) of 111.[4]

The Isotonic Solutions and Major Adverse Renal Events (SMART) trial[5] was published alongside SALT-ED in the same issue of the NEJM. This trial compared NS with BC in ICU patients admitted to one of five ICUs at a single academic centre. Each ICU was randomized to utilize either NS or BC for one month at a time, switching every month. A total of 15,802 adults were randomized, 7942 in the BC group and 7860 in the NS group. Each group received similar volumes of fluid on average, although the range was large (0-3500ml). The primary outcome used the same MAKE30 composite criteria as in SALT-ED. Similarly to SALT-ED, this trial showed a significant decrease in MAKE30 in the BC group, with a NNT of 91. Within the subset of patients admitted with sepsis, the BC group had significantly less mortality at 30 days, as well as significantly less MAKE30.[5]

While both trials showed that patients receiving BC had significantly lower rates of adverse events as defined by the MAKE30 outcome,[4,5] it is worth considering that as a composite outcome comprising death, need for initiation of renal replacement therapy, and a doubling of serum creatinine, critical thought should be applied regarding its validity. These component outcomes are not clinically equivalent, but were treated equivalently in the analysis. In SALT-ED, the differences observed were driven largely by differences in renal failure, and showed that even low to moderate doses of saline may be particularly harmful for patients with pre-existing renal injury.[4] By contrast, the harmful effects of NS in SMART were driven largely by a difference in mortality (11.1% vs. 10.3%, p=0.06). Subgroup analysis revealed even greater differences in mortality for patients receiving NS with sepsis (29.4% vs. 25.2%, p=0.020) or who were already receiving chronic dialysis (18.4% vs. 12.2%, p=0.015).[5] Although not the primary goal of this trial, these analyses of the components of the MAKE30 outcome suggest that these populations may be particularly sensitive to crystalloid selection and that further study is needed.

The SMART and SALT-ED trials represent the most significant efforts yet undertaken to discern whether NS or BC solutions are superior for crystalloid fluid therapy. The significant sample sizes meant that both trials were powered to detect small differences in outcomes, an important factor when considering the ubiquity of crystalloid fluid resuscitation. The SMART trial is also exceptional among ICU trials

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for randomizing patients within the ED, allowing for the assigned fluid to be delivered early.[5] However, there are identifiable limitations in each trial. Both trials included only a single academic centre, and neither blinded clinicians to group assignment. This has the potential to affect decisions such as the initiation of renal replacement therapy and could introduce an element of treatment bias. Plasma-Lyte and lactated Ringer's were also considered together in both trials, meaning that clinicians will have to await further investigations to inform the choice between these two options. An additional drawback in the SMART trial is in regards to its study population, which included ICU patients. The need for continuous IV fluid administration in ICU patients meant that those who remained in the ICU at the end of one calendar month may have been exposed to both NS and BC without a washout period. According to the authors, this occurred in only 4.4% of NS group and 5.4% of the BC group,[5] however it is conceivable that this switch could affect the results. Finally, SMART did not have a patient-centred primary outcome. While subgroup analysis did reveal possible signals towards reduced mortality in certain patient subgroups receiving BC, more evidence is needed before drawing conclusions about fluid choice and mortality.

There are currently two large multicenter randomized controlled trials in progress in Australia[6] and Brazil[7] comparing Plasma-Lyte to NS in ICU patients. Neither trial plans to recruit as many patients as SMART or SALT-ED, but both list 90-day all cause mortality as a primary outcome.[6,7] Additionally a very large trial (planned N=65,000) currently underway in Canada will compare NS to lactated Ringer's in all hospitalized patients.[8] Clinicians will eagerly await the results of these trials, but in the meantime SMART and SALT-ED provide the best evidence to guide crystalloid therapy. For patients admitted to the hospital outside of the ICU, SALT-ED suggests that the choice of crystalloid did not affect hospital-free days, while secondary analysis points towards a possible advantage for BC in avoiding kidney dysfunction.[4] In patients admitted to the ICU, SMART showed that BC significantly reduced adverse MAKE30 outcomes, with a particular benefit in those with sepsis.[5] Ultimately for patients not requiring ICU admission, clinicians must still rely on their clinical judgment when choosing a crystalloid fluid. For clinicians attending to patients in the ICU, the findings of SMART suggest a move towards BC over NS for most patients requiring fluid resuscitation.

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