Is Normal Saline Solution an Acceptable Choice of Fluid for Stable Patients?

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Isotonic 0.9% sodium chloride solution (normal saline solution) is the most commonly used intravenous fluid in much of the world, including North America.[1] Laboratory evidence of deleterious effects of normal saline solution has accumulated during the last few decades.[2] The clinical influence of these findings has been of concern, given the wide use of intravenous fluid therapy. Most clinical research on this question has been performed in perioperative, hospitalized, and critically ill patients, including 2 recent, large, single-center, multiple-crossover trials.[3,4] In these studies, a balanced crystalloid solution (lactated Ringer's solution) was associated with fewer major adverse kidney events (death, new renal replacement therapy, or persistent renal dysfunction) than normal saline solution in both ICU patients and emergency department (ED) patients who were subsequently hospitalized in non-ICU settings. Approximately 85% of ED patients are discharged home, however, and the applicability of these findings to this group of less seriously ill patients is unclear.[5]

In this issue of *Annals*, Friederich et al[6] report the results of a small, single-center, randomized trial of normal saline solution versus lactated Ringer's solution for ED patients whose clinical team had ordered intravenous fluid, who were judged to be able to tolerate a 2-L bolus of fluid, and who were expected to be discharged home. Patients were young (median age 33.5 years), had few comorbidities, and presented with chief complaints typical of those for which intravenous fluid is ordered (eg, abdominal pain, nausea, vomiting). Pregnant patients, those with jaundice, and those undergoing chemotherapy were excluded. The investigators found no differences between the 2 groups in the primary outcome of patient-reported recovery (using a survey instrument previously validated in anesthesia and surgery patients) or in secondary outcomes measuring further health care use.

How should these results be interpreted? The weaknesses of this study include the nearly 40% loss to follow-up for the primary outcome, a small sample size, a single-center design, and the use of a survey instrument that had not previously been validated for ED patients. However, no differences in outcome were observed despite a volume load that was twice that administered in the 2 recent large trials.[3,4] These trials also suggested that normal saline solution may be more harmful in sicker patients. Although both trials observed increased major adverse kidney events with normal saline solution, the most common individual adverse event was death in the ICU patients[4] versus persistent renal dysfunction in the ED patients who were hospitalized but did not require ICU admission.[3] It is thus plausible that in less ill patients, such as those enrolled by Friederich et al, normal saline solution may be less harmful or not harmful. Previous studies of normal saline solution infusion in healthy volunteers primarily examined physiologic outcomes such as renal blood flow velocity, but not clinical outcomes.[7]

What are the potential clinical implications? This trial provides some reassurance that normal saline solution is an acceptable choice of fluid in ED patients who are young, are stable, have minimal comorbidities, are able to tolerate a 2-L intravenous fluid bolus, and are expected to be discharged home. Despite the carefully chosen eligibility criteria, however, 18% of these patients were hospitalized and may have been at higher risk of adverse renal events.[3] Because it is difficult to predict the need for hospitalization for every patient, the choice of balanced fluid as a default for all ED patients thus appears reasonable, whereas normal saline solution may be acceptable for individuals for whom discharge from the ED appears certain.

What is clear is that there is equipoise for the question of which fluid is associated with better outcomes in stable ED patients. It thus seems desirable for future trials to

randomize subjects to either normal saline solution or balanced fluids. The study by Friederich et al was not designed to measure subsequent renal function as an outcome. Given the expected low incidence of renal dysfunction in patients discharged from the ED, however, any effect size would likely be small. Indeed, the absolute reduction in major adverse kidney events in the large trial of hospitalized ED patients was 0.9%, with a number needed to treat of 111.[3] Moreover, measuring postdischarge renal function is likely to be challenging. Thus, future studies should aim to increase sample size and decrease loss to follow-up, as well as attempt to expand the range of outcomes to be measured, including renal function. A tighter integration of clinical care and clinical research may facilitate the successful execution of such trials.[8]

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