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Making the Medicine Go Down: Salt or Sugar?

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What should we expect from a medication diluent? In current critical care practice, we expect diluents to keep medications stable for administration and to infuse alongside other drugs compatibly. But is that enough? Millions of critically ill adults are exposed to intravenous (IV) medication diluents each year – and yet few studies have examined the effect of diluent composition on patient outcomes.

In this issue of *Critical Care Medicine*, Magee and colleagues¹ take an important first step toward understanding the potential effects of IV medication diluent composition on clinical outcomes for critically ill adults. In a before-and-after trial enrolling 426 patients from a single medical intensive care unit (ICU), the authors compared the two most common diluents: 0.9% sodium chloride (saline) versus 5% dextrose in water (D5W). The study reports two primary findings. First, 63% of the IV fluid volume received by patients in the ICU came from medication diluents (rather than from fluid given for resuscitation or maintenance of intravascular volume). While slightly higher than prior studies,^{2,3} this finding confirms that fluid volumes from medications are not trivial. In fact, the volume of fluid received from diluents in this study is comparable to the volume of resuscitation fluid that produced differences in renal function and mortality in other recent fluid management trials.^{4–6} Second, use of D5W rather than saline as the primary diluent was associated with less hyperchloremia, a numerically lower incidence of acute kidney injury, and similar rates of hyponatremia, hyperglycemia, and insulin receipt.

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Editorial on “Insidious harm of medication diluents as a contributor to cumulative volume and hyperchloremia: a prospective, open-label, sequential period pilot study” (CCMED-D-17-01215R2)

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These findings are plausible. The 154 mmol/liter of chloride contained in saline has long been known to cause hyperchloremia and metabolic acidosis when used for resuscitation.^{7–9} Studies of human volunteers suggest saline causes renal vasoconstriction⁸ and observational studies among critically ill adults have associated saline administration with acute kidney injury, renal replacement therapy, and death.^{10,11} Just recently, our research group demonstrated a higher incidence of death, new renal replacement therapy, or persistent renal dysfunction with saline compared to balanced crystalloids in two clinical trials enrolling nearly 30,000 acutely ill adults.^{6,12} It is not unreasonable to think that the chloride load delivered by intravenous fluid might have a similar effect on serum electrolytes, acid-base, renal function, and patient outcomes whether the fluid is given to expand intravascular volume or as a medication carrier.

Important limitations of the study by Magee and colleagues, however, must be noted. The study is relatively small, and may be underpowered to detect clinically meaningful differences in laboratory or clinical outcomes. A larger study would be required before definitively concluding that using D5W rather than saline as the primary diluent does not increase the incidence of hyponatremia, hyperglycemia, or insulin receipt. The before-and-after design introduces potential biases, especially selection bias and risk for secular changes in patient care over time. More patients in the D5W period than the saline period were admitted from the floor, and baseline values for serum sodium and chloride concentration differed significantly between the groups. The volume of saline given as an IV fluid bolus for resuscitation was greater in the saline period than the D5W period – a key confounder when attempting to isolate the effect of saline as a diluent on outcomes.

So, which should be the primary medication diluent in the ICU: saline or D5W? The argument in favor would of D5W would be: (1) medication diluents are ubiquitous in critical care, (2) the volume of fluid contributed by diluents is enough to potentially impact patient outcomes, (3) recent data suggest saline may contribute to renal dysfunction and mortality, and (4) the current study suggests D5W may be a safe alternative to saline associated with less hyperchloremia, and by extension perhaps less acute kidney injury and death. Taking the long view, however, our answer is that *neither* saline nor D5W should be the primary medication diluent in the ICU. Saline and D5W have been the primary medication diluents for decades because of stability, compatibility, and availability – not because they are necessarily optimal for patients. Switching from saline to D5W risks trading one set of problems (e.g., hyperchloremic metabolic acidosis, kidney injury, death) for another (e.g., hyponatremia, hyperglycemia, metabolic acidosis). Importantly, the strong ion difference for both saline and D5W is zero, so *both* fluids may worsen acidosis.

Instead, we should expand what we expect from a medication diluent. The ideal diluent should keep medications stable for administration, infuse compatibly alongside other drugs, *and* contain a chemical composition without potential detrimental impact on patient's acid-base status, organ function, or clinical outcomes. “Balanced crystalloids” such as lactated Ringer’s solution or Plasma-Lyte may represent one answer to this challenge. Balanced crystalloids contain a more physiologic electrolyte and acid-base composition than saline or D5W, and appear to improve clinical outcomes compared to saline when used for resuscitation.^{6,12} Historically, balanced crystalloids have not been widely used as medication

diluents due to lack of compatibility testing, lack of commercially available appropriate volume sizes, and concern about the interaction of medications with their electrolytes (e.g., calcium, magnesium) and buffers (e.g., lactate, acetate, gluconate). Few of these concerns, however, are based on solid empiric evidence. For example, current guidelines recommend against the use of calcium-containing balanced crystalloids with blood transfusions¹³ despite evidence suggesting lactated Ringer's can safely be infused in conjunction with packed cell transfusions.¹⁴

With growing uncertainty over the safety of saline as the primary diluent among critically ill adults, and the potential shortcomings of D5W as a substitute, we should move quickly to explore the utility of balanced crystalloids as medication diluents. First, by examining the acid and base reactive groups on organic drug molecules and pH ranges at which those groups are predominantly ionized or non-ionized to deduce, predict, and preclude drug-diluent incompatibilities.¹⁵ Second, by applying the rigorous, prospective, controlled research to diluents that has advanced our understanding of resuscitation fluids. Magee and colleagues have shown a spotlight on an important exposure received by millions of critically ill adults around the world for which we have next to zero clinical evidence to inform best practice. We owe it to our patients to develop and test diluents that are optimal not just for drug stability and compatibility, but for patient outcomes.

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