Balanced crystalloids for the critically ill: knowledge on the rise but confusion still reigns!

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In a recently published retrospective study including a large cohort of postoperative and critically ill patients admitted in intensive care (IC), Zampieri *et al.* reported an association between infusion of a higher percentage of Lactated Ringer (LR) solution and less occurrence of acute kidney injury (AKI) and a reduced hospital mortality (1). The "protective" effect of LR was more pronounced as the total administered volume increased. Surviving patients received proportionally more LR and less normal saline (NS) than non-survivors.

At first sight, this study feeds the growing belief among IC physicians that NS infusion should be abandoned as standard resuscitation fluid and replaced by so-called balanced crystalloid solutions. However, the reality is much more complex. Volume loading indisputably is a crucial part of treatment in the critically ill. Anyhow, it remains an "invasive metabolic assault" with potentially significant disruptive effects on plasma and extracellular acid-base homeostasis. A controversial but fairly comprehensive viewpoint on acid-base equilibrium that elegantly "captures" this process is the Stewart approach. According to Stewart, the most important independent variable dictating the acid-base status of (body) fluids is the apparent strong ion difference (SIDa) (2). As a rule, a decrease in SIDa results in metabolic acidosis. Plasma has a SIDa of 42 mmol/L. In contrast, NS has a SIDa of zero because it contains similar strong cation (Na^+) and strong anion (Cl^-) concentrations. Thus, too liberal or abundant NS infusion not only will challenge the extracellular environment with a high chloride burden but also cause "dilution" of the plasma and extracellular SIDa (3). The resulting hyperchloremic metabolic acidosis is thought, at least in experimental sepsis, to enhance systemic inflammation, to alter the microcirculation, and to adversely affect kidney function (4-6). Hyperchloremic acidosis can be prevented by introducing balanced crystalloid fluids in which the culprit chloride anion is substituted by strong anions such as lactate in RL or gluconate/acetate in Plasma-Lyte®. These solutions are considered to be "balanced" because they contain much less chloride than NS and have a SIDa lower than that of plasma but higher than zero.

The current study adds to the controversy that dominates the ongoing debate on whether to use balanced liquids or NS as primary volume treatment. In fact, the findings of Zampieri *et al.* are not entirely in agreement with those of Van Regenmortel *et al.* who recently published a retrospective study in an equally large mixed cohort of IC patients (7). These authors reported that severe hyperchloremia (>110 mmoL/L) but not a low SIDa was associated with increased IC mortality. In the Zampieri study, lower chloride levels at admission were observed in hospital non-survivors. Moreover, volume-adjusted chloride load (VACL) had no impact on mortality and the percentage infused LR remained associated with better survival in those patients receiving a VACL within normal physiological range (1). This suggests that a fluid-related effect was not

determined by the chloride content but rather by the (lower) SIDa of the solution.

The suggested preventive effect of balanced crystalloids in general and LR in particular on the occurrence of AKI is even less obvious. Patients who developed AKI in the Zampieri study received proportionally less LR. However, the proportion of NS was similar between AKI and non-AKI patients and VACL was not associated with AKI after adjusting for covariates (1). Van Regenmortel *et al.* also did not observe an increased prevalence of hyperchloremia in patients who developed AKI (7). This corroborates with previous clinical studies that found no difference in incidence of AKI, need for renal replacement therapy, and kidney-related mortality among IC patients who received similar amounts of NS and balanced crystalloids (8,9).

One can only speculate about the reasons underlying the differences in outcome between the Zampieri and Van Regenmortel studies. Despite their retrospective design, both studies provide an adequate "real-life" blueprint of fluid therapy in postoperative and critically ill IC patients. The studies differ in patient population (e.g., more heart failure and an unspecified number of sepsis patients in the Van Regenmortel study), disease severity (important divergence in baseline severity of illness), and in defining AKI (RIFLE versus KDIGO). More importantly, however, the study of Van Regenmortel *et al.* lacks information on type and volume of fluids and did not record VACL (7). In contrast, Zampieri *et al.* decomposed the individual effect of specific fluid types on mortality and also demonstrated that the composition of a particular fluid becomes a matter of importance when increasing amounts of that fluid are infused (1).

In conclusion, the impressive work of Zampieri *et al.* certainly contributes to a better understanding of volume management in IC patients, in particular with regard to fluid type and volume. However, the study leaves many questions open or unsolved. A potential detrimental effect of fluid-induced hyperchloremia on outcome in clinical conditions remains uncertain. Any harmful effect of NS on kidney function is insufficiently supported. Finally, it remains to be proven how infusion of Plasma-Lyte®, a balanced crystalloid with an almost twofold higher SIDa than LR (50 *vs.* 27) (3), affects relevant outcome parameters. Prospective studies are definitely needed that either compare NS with balanced crystalloids or balanced solutions mutually. These studies should focus on relevant and well-defined outcome parameters in IC patients while taking into account important parameters associated with fluid treatment such as volume load, pre- and post-infusion chloride concentrations, and effects on host acid-base status (e.g., by analyzing SIDa).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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