Editorial

The good receipt for the kidneys: salty…but not too much

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After its first application in 1831, during the second cholera pandemic (1), "normal" saline has become one of the most commonly used crystalloid solutions worldwide (2) and over one million litres are administered intravenously everyday (1). Nevertheless, the non-physiological composition of the 0.9% saline and its related risks of kidney injury have recently alarmed intensivists and other clinicians and the so called "balanced crystalloids" have been studied as safer alternatives. On this regard, the German guidelines on "Intravascular Volume Therapy in Adults", recently published in the European Journal of Anaesthesia (3), addressed the "*Differences between crystalloids in Intensive Care Unit (ICU) Patients*". With an "A" Grade of Recommendation (strong) it has been indicated that "*An isotonic saline (i.e., NaCl 0.9%) solution must not be used as a volume substitute in intensive care medicine*" (3). In the background section, the authors underline that balanced crystalloid solutions are associated with a lower incidence of hyperchloremic acidosis and lower renal dysfunction in comparison with isotonic saline. In support of this statement, two studies are cited: the first is a single-centre, two-arm, double-blind, randomized trial performed in 42 patients with traumatic brain injury or subarachnoid hemorrhage that showed a 95% incidence of hyperchloremic acidosis in the saline group *vs.* 65% in the balanced group after 5,000 mL in both groups over 48 hours (hazard ratio =0.28; 95% CI: 0.11, 0.70; P=0.006) (4). The second study, by Yunos *et al.* has been published in the Journal of American Medical Association in 2012 (5). It is a prospective open-label before and after pilot study on about 1,400 patients that demonstrated that treatment with chloride-rich solutions (0.9% saline, 4% succinylated gelatin solution, or 4% albumin solution) was associated with a significantly higher serum creatinine level (P=0.03), an increase in the incidence of renal insufficiency (P<0.001) and a greater need for renal replacement therapy (RRT) (P=0.004) in comparison with the time-period when chloride-poor solutions (balanced solutions or chloride-poor 20% albumin) were administered, after adjustment for multiple covariates (5).

With this background, safety concerns arose about the use of saline in critically ill patients and other non-randomized studies and meta-analyses seemed to confirm that high chloride content of saline may contribute to the development of acute kidney injury (AKI), increase the need for RRT, and even rise the mortality rate (6,7). In light of these effects on renal function, balanced solutions with lower, more physiologic chloride concentration, have been suggested (1,4). In order to fill this significant gap in scientific literature, Young *et al.* recently published a double-blind, cluster randomized, double-crossover trial (8) (Saline versus Plasma-Lyte® 148 for ICU fluid Therapy, SPLIT, trial) on 2,278 patients admitted to 4 general medical and surgical ICUs (one of them mainly admitted patients with cardiothoracic and vascular diseases) requiring crystalloid fluid therapy. Patients randomly received either buffered crystalloid (Plasma-Lyte 148®; B-group; 1152 patients) or saline (NaCl 0.9%; S-group; 1110 patients), according to clinical indication, as maintenance therapy or fluid volume replacement. The trial was specifically designed to evaluate the proportion of patients with AKI (serum creatinine level rise of at least 2-fold or a serum creatinine level of ≥3.96 mg/dL with an increase of ≥0.5 mg/dL) as primary outcome, RRT use, change in serum creatinine (Δ creatinine), need for and duration

of mechanical ventilation, ICU readmission, ICU length of stay, and ICU and in-hospital mortality as secondary outcomes. Surprisingly, the use of a buffered crystalloid compared with saline did not reduce the risk of AKI (9.6% of B-group patients *vs*. 9.2% of S-group patients; P=0.77) at 90-day follow-up. In addition, no significant between-group differences were observed in any of the secondary outcomes.

This well conducted trial should be carefully appraised before reaching any "new" conclusion or recommendation for the clinicians, in order to avoid any confusion and apparent uncertainty on the effects of fluid type administration.

First, both groups had few comorbidities and overall patients' outcomes, regardless of the randomized intervention, was unlikely representative of many ICUs case mix. The Acute Physiology and Chronic Health Evaluation II score was 14.1 in both groups, the ICU mortality was 6.6 and 7.2% and the RRT rates 3.3 and 3.4% in B and S-groups, respectively. As a demonstration of the low-severity of illness, Hoste and co-workers, in a recent epidemiologic study (Acute Kidney Injury-Epidemiologic Prospective Investigation; AKI-EPI) found that in 33 different countries on five continents and 97 ICUs, out of 1,802 patients, 57.3 % had AKI, 23.5 % of them received RRT, and 13.5 of all patients received RRT (9), a significantly higher incidence than in Young *et al*.'s study. As far as the case mix of enrolled patients is concerned, furthermore, most patients of the SPLIT trial underwent cardiothoracic and vascular surgeries. Post-surgical patients may be very different from critically ill patients with multiple organ failure in which many nephrotoxic factors (e.g., anemia, hypotension, vasopressors, nephrotoxic antibiotics etc.) may co-act significantly increasing the risk of AKI (10). Specifically, use of contrast media and nephrotoxic drugs (e.g., vancomycin or aminoglycosides), independent predictors of nephrotoxicity in the critically ill, were not evaluated in the SPLIT trial (8).

Secondly, the median administered volume of each fluid was low quite low (about 2,000 mL in both the B and S-groups; P=0.63) during the ICU stay, and most of the fluid administration occurred during the first 24 hours as clearly underlined by the accompanying Editorial (11). In view of this observation, some general pathophysiological considerations should be highlighted: (I) the restricted fluid therapy, when adequately balanced between hypovolemia and excessive weight gain, has shown to be, *per se*, useful in reducing AKI incidence (12)—this approach, carefully applied in Young's study might have somehow blunted the negative effects of the nephrotoxic fluid; (II) the possibility of infusing low volumes of fluids may indirectly confirm the low severity of illness of enrolled patients and a good integrity of the endothelial glycocalix and microcirculation (13)—this is generally not the case in conditions of severe inflammatory states (e.g., sepsis); (III) the development of metabolic acidosis [also described as hyperchloremic acidosis or strong ion difference acidosis (14)], as well as the decrease in kidney cortical perfusion were demonstrated after rapid administration (bolus) of 2,000 mL of saline in healthy subjects (15,16) or after 70 mL/Kg in 2 hrs after surgery (17). Toxicity, in general, is dose dependent and the consequences of the exposure depend on the susceptibility of the patients, as for all the other substances present in nature, water included (18). Serum chloride concentrations were not reported in the study by Young and colleagues (6). Therefore, it could be argued that the negative (mainly renal) effects of chloride loading might be more pronounced, and therefore easier to be demonstrated, in sicker patients, with more limited renal functional reserve, who receive larger chloride amounts with replacement fluids. In other words, the only fact that I prepare a cake with lowest doses of a toxic substance without causing gastro-enteritis to people who taste it, does not necessarily mean that this receipt is safe.

Third, in the SPLIT trial, the renal injury was investigated with serum creatinine levels only, according to RIFLE and KDIGO criteria. Possibly, although the SPLIT trial has been specifically designed to test the effects of two different fluid preparations on renal function, the authors did not investigate subclinical forms of renal dysfunction that might be induced by chloride-rich solutions (19). It is well known that the so called renal functional reserve, in healthy subjects, must be exhausted before serum creatinine increases (11,20). Since creatinine has a much lower sensitivity than other recently identified biomarkers, it could be supposed that different methods of investigation, could have revealed renal reserve reduction, otherwise missed by the simple creatinine rise (21). In fact, some novel biomarkers appear to be positive even in to "subclinical AKI" where creatinine does not increase (22,23). Moreover, the RIFLE classification also includes urine output criteria, that has not been included in the SPLIT trial. The only use of serum creatinine alone has shown to potentially underestimate the incidence and grade of AKI and delay the diagnosis in critically ill adult patients (10).

As a final consideration, however, it must be remarked

that the SPLIT trial clearly provided some support on the fact that the administration of a relatively low volume of 0.9% saline to low/moderate risk ICU patients, does not cause clinically significant, or demonstrable, harm.

Conclusions

Fluids are the most frequent therapy administered to critically ill patients as for rehydration, as a carrier for medications, and as volume expander for hemodynamic optimization. Nonetheless, which is the best fluid composition is still an unsolved debate and there is a wide variation in clinical practice with respect to the selection of resuscitation fluids (2). Undoubtedly, large-scale randomized trials are still required to demonstrate which crystalloid solution is superior over the other in specific clinical conditions. What should always be considered with great attention is whether are we justified, in the absence of specific electrolyte deficit (i.e., sodium or chloride), to administer a non-physiologic fluid that likely causes harm even if not clinically or laboratory visible. Since safer alternatives exist, in the need of administering large volumes of fluids to critically ill patients, 0.9% saline should probably be avoided (24).

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Footnote

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