Editorial

Intravenous sodium and chloride: not too much, not too quick, and only to healthy kidneys!

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Although the first clinical use of a fluid therapy based on sodium chloride dates back to the European cholera pandemic in 1831 (1), the first clinical study focused on the acid-base equilibrium in patients receiving NaCl 0.9% (or saline or normal saline) for volume expansion was published in 1999 and was entitled "Rapid Saline Infusion Produces Hyperchloremic Acidosis in Patients Undergoing Gynecologic Surgery" (2). This landmark study aimed at evaluating the effects of the administration of saline, a high chloride concentration crystalloid, in clinical practice. The authors investigated the acid-base equilibrium effects derived from the rapid high volume infusion (about 70 mL/kg in 2 hours) of saline versus lactate Ringer's solution in women undergoing gynecological surgery. After the infusion of such amount of fluids, consistent abnormalities in acid-base equilibrium were evident in the saline group: a dramatic drop in pH (from 7.41 to 7.28), base excess (from –0.4 to –6.7 mM), an increase in serum chloride concentration (Cl^-) (from 104 to 115 mM), and, importantly, a significant decrease (–9 mM) in strong ion difference (SID) [strong cation concentrations (e.g., sodium, potassium, magnesium)—the strong anion concentrations (e.g., chloride and lactate)]. The observed acid-base derangements are now widely known as hyperchloremic acidosis or SID acidosis (3). "Normal" saline is non-physiological in three ways: (I) the level of chloride is significantly above that of plasma (154 versus 110 mEq/L); (II) it lacks several electrolytes normally present in plasma, including potassium, calcium, glucose, and magnesium; (III) it lacks the bicarbonate or any buffer necessary to maintain its pH within normal limits. Saline composition was first mentioned by the Dutch physiologist Hartog Jacob Hamburger in the 1890s (4): the term "normal saline" itself appears to derive from the observation of *in vitro* studies on red cell lysis that incorrectly identified 0.9% as the concentration of salt in human blood rather than 0.6%, the actual concentration (1). Unfortunately, the diffusion of the terminology 'normal saline' may have contributed to the widespread acceptance of 0.9% saline into clinical practice. Despite this, saline is far from being physiologic: its high chloride concentration causes its SID to be 0 {deriving from [154 (Na^+) – 154 (Cl^-) mEq/L]} and significantly different from plasma (40 mEq/L) (5). According to the Stewart physiochemical approach to acid-base balance, plasma pH changes also depending on the SID. Therefore, when significant doses of saline are administered (e.g., 30 mL/kg) a significant drop in plasma SID occurs leading to hyperchloremia and metabolic acidosis. Over the last ten years, a consistent body of literature has shown the potential adverse clinical consequences of saline utilization as resuscitation fluid compared to buffered crystalloids (e.g., Hartmann's solution, Plasma-Lyte, Lactates Ringer's Solution) (6-11). Overall, existing data from observational studies and large prospective randomized trials, clearly indicate that the use of high chloride unbuffered crystalloid fluid is eventually associated with negative outcomes,

including major adverse kidney events (MAKE) and increased mortality in critically ill (6,11) and noncritically ill (10) patients. The hypothesized mechanisms for acute kidney injury (AKI) following hyperchloremia involves adenosine 1 receptor-mediated vasoconstriction in afferent arterioles in kidney (activation of the tubulo-glomerular feedback) (12) leading to a decrease in renal blood flow and perfusion, thereby causing reduction of the glomerular filtration rate and urine output (10,13). In addition, the decrease in plasma pH may increase afferent arteriolar resistance in kidney leading to further deterioration of renal function. In a recent issue of the *Journal of Thoracic Disease*, Lim *et al.* have retrospectively investigated the incidence of AKI following saline administration after cardiac surgery performed with cardiopulmonary bypass (CPB) (14). Two patients' groups were identified and analyzed: during the first postoperative 48 hours 328 patients (18.8%) received over 1 L of saline (high-volume group) and 1,412 (81.2%) less than 1 L (low-volume group). Secondary outcomes were new onset of renal replacement therapy (RRT) and early (in-hospital) mortality. Globally, the high-volume group received 2.47±1.51 L of saline and the low-volume group 0.54±0.32 L. Similar amounts of balanced solutions and colloids were administered to the patients. The authors did not find significant differences in the explored primary and secondary outcomes. Age, CPB time, fresh frozen plasma (FFP) transfusion, and postoperative extracorporeal membrane oxygenation (ECMO) support were identified as risk factors for the three outcomes. A couple of years before, a cluster randomized, double-crossover trial, entitled "Effect of a buffered crystalloid solution *vs.* saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial", was published by Young *et al.* (15). Similarly to Lim *et al.*'s study, no difference in the prevalence of AKI, in-hospital mortality, or use of RRT within 90 days after enrollment were found in a heterogeneous population of intensive care unit (ICU) patients who received a buffered crystalloid or saline (15). The saline load in Young *et al.*'s study was modest and, noteworthy, quite similar to the exposure of Lim *et al.*'s high volume patients (about 2 L in both studies). It is possible to assume that the total exposure to saline, and specifically chloride, was unlikely a sufficient amount to determine a plausible hazard in the explored populations. Although the single patients' population susceptibility of Lim *et al.*'s study is not easy to extrapolate, the absence of severely depressed left ventricle ejection fractions (58.0%±10.9%), the apparently normal baseline creatinine values [0.9 (0.75–1.09) mg/dL], the normal glomerular filtration rates (74.4±31.5 mL/min/1.73 m^2) might globally indicate a relatively low risk for kidney failure mostly related to age, CPB time, FFP transfusion, and postoperative ECMO as shown by the multivariable analysis (14). The relatively low incidence of AKI in both groups, 31/328 (9.5%) and 126/1,412 (8.9%) in the high and low volume groups respectively, lower than those found after cardiac surgery in many trials (16), might support our hypothesis. Interestingly, overall, development of AKI was similar to the incidence observed in the SPLIT trial within 90 days of enrollment (15). A crucial aspect that must be underlined is that the high chloride concentration of the normal saline eventually leads to hyperchloremia and acidosis only if the solution is administered fast enough and in large volumes (5). As a matter of fact, however, controversial results have been found in literature regarding AKI, dialysis requirement, and mortality with authors showing significant harm when saline is given as resuscitation fluid (6,9-11) while other studies showed no substantial difference in comparison with more balanced solutions (14,15). This apparent contradiction can be explained in terms of inherent toxicity of a solute: toxicity depends on the combination of three factors, i.e., the dose and the speed of the delivered substance and the susceptibility of the exposed population. Clearly, the higher the susceptibility of the population the lower the dose needed to clinically manifest the injury. Furthermore, it appears evident that, in a 70 kg patient, 1 L of saline over 3 days will exert significantly different effects from 5 L delivered in few hours. The recent studies that have highlighted the toxic effect of chloride loading (6,10,11) implied significantly higher volumes of saline administration in comparison with Lim *et al.*'s study and Young *et al.*'s study; also, critically ill patients' and emergency department patients' susceptibility was higher. For instance, the study by Sen *et al.* (6), found an expected relationship between chloride load and total mean volume of fluid administered in 24 hours and, importantly, between the saline load and the incidence and severity of AKI: those who received 3.7 (95% CI, 3.2–4.2) L of NaCl 0.9% (first quartile) showed an AKI incidence of 72.1% (21.7% stage 3 KDIGO), whereas those who received 8 (95% CI, 6.8–10) L (fourth quartile), an AKI of 86.1% (42.5% stage 3 KDIGO). Moreover, the authors found a correlation between saline volume received and hospital mortality: 19.2% and 35.4% in first and fourth quartile, respectively. In this trial, large-volume resuscitation was defined as 60 mL/kg or greater of normal

saline in a 24-hour period. In Lim *et al.*'s study, saline administration in the high-volume group was roughly about 20 ml/kg in a 70 kg patient in 24 hours. The two other recent large trials, the Saline against Lactated Ringer's or Plasma-Lyte in the Emergency Department (SALT-ED) trial (10) and the Isotonic Solutions and Major Adverse Renal Events Trial (SMART) (11), have further confirmed the toxic potential of chloride load. In the first trial noncritically ill patients admitted from the emergency department to a hospital ward and in the second one critically ill patient admitted from the emergency department, operating room, or general ward to an ICU were assigned to balanced or saline solutions. Patients in both trials did not receive high volumes of either balanced crystalloids or saline. Nevertheless, in both trials, patients who received saline showed significantly higher serum concentrations of sodium and chloride. In both trials, the use of saline was associated with a significant increase in the composite outcome of death from any cause, new RRT, or persistent renal dysfunction while no significant differences in short term mortality or in the use of RRT were observed. In noncritically ill patients, the treatment effect was greater in patients who had baseline hyperchloremia or a serum creatinine above 1.5 mg/dL on presentation. In the critically ill patients in the SMART, the entire associated with balanced fluids for both the composite outcome and mortality was mostly evident in patients with sepsis and with higher predicted in-hospital mortality: the overall number needed to treat to prevent the composite outcome was 91, whereas among patients with sepsis it was 20 (17). These observations confirm the harm related to chloride load in patients at higher risk because more susceptible. Alternatively, it might be hypothesized that patients with preserved kidney functional reserve could mask, at least form a creatinine increase and/or urine output decrease point of view, the toxicity of NaCl. Finally, even if the issue of detrimental effects of both hypovolemia and fluid overload are beyond the scope of this paper, Lim *et al.* correctly state that "…the beneficial effect of hydration with high-volume infusion of saline may outweigh the potential adverse effect of hyperchloremic metabolic acidosis that may result from saline infusion". Nevertheless, are we, as clinicians, justified, in the absence of specific electrolyte deficit (i.e., sodium or chloride), to prescribe the non-physiologic fluid, likely causing harm, even if in some cases this is not clinically manifest? Over the last years, administration of intravenous fluids in surgical and critically ill patients has been based on physiological hemodynamic principles rather than on evidence from clinical trials. More recently, large randomized studies have shown that fluids may harm some specific patients' populations: colloids such as albumin are associated with increased mortality among patients with traumatic brain injury (18), and hydroxyethyl starch is associated with AKI, RRT and mortality in septic patients (19). As a logic consequence, crystalloids, including normal saline, have been preferred over colloids in the major part of surgical and ICU patients. Although none of the currently available resuscitation fluids are actually "physiologic", the evidence that a fluid therapy based on supraphysiologic chloride concentrations (like saline) has been associated with hyperchloremia, acidosis, and a higher incidence of complications (e.g., MAKE) and mortality when compared to balanced crystalloids is progressively growing. Studies that have investigated the administration of a plausible dose of saline to a population at sufficient risk for adverse outcomes were able to uncover the hazard. This hazard will remains hidden when low-risk patients receive insufficient doses of fluids.

In conclusion, the study by Lim and collaborators is well conducted with excellent adherence to study protocol and interesting results. Their data provide reassurance that saline does not appear to be particularly harmful if administered in a modest dose spread in 48 hours even after cardiac surgery with CPB. Nevertheless, since safer alternatives exist, standard resuscitation fluid therapy should specifically include balanced crystalloid solutions and saline administration should probably be limited to hyponatremic and/or hypochloremic patients (20).

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Footnote

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