Isotonic saline, balanced fluids and chloride toxicity in ICU: lessons from the PLUS trial.

Laurent Muller1, Olivier Joannes-Boyau2.

Affiliations :

1IMAGINE, UR UM 103, Univ Montpellier, Service des Réanimations, Pôle Anesthésie Réanimation Douleur Urgence, CHU Nîmes, Montpellier, France

2Service d'Anesthésie-Réanimation Sud, Centre Médico-Chirurgical Magellan, Centre Hospitalier Universitaire (CHU) de Bordeaux, 33000 Bordeaux, France

Keywords : fluids, acute kidney injury, fluid filling, ICU, saline, balanced crystalloids,

The potential harmful effects of isotonic saline overuse during fluid infusion have been evocated for more than 100 years1 but poorly investigated until the end of 90’s2. In recent human experimental models, infusion of isotonic chloride significantly impairs renal perfusion by direct vasoconstriction as compared to isotonic balanced crystalloids, which could lead to acute kidney injury (AKI)3,4. In hospital, AKI is frequent, ranging from 10 to 20% of all patients to about 50% in Intensive Care Unit (ICU). It is also a severe syndrome, with an associated-mortality rate close to 50 % at one year5,6. The AKI rates can be prevented by two ways. First, a rapid control of main AKI causes such as sepsis, shock, hypovolemia, low cardiac output, surgery duration, urinary tract obstruction helps to early AKI resolution and prognosis improvement. Second and concomitantly, limiting the use of drugs that potentially impair renal function is also necessary. In 2 large retrospective studies, the limitation of isotonic saline use and a subsequent shift to balanced solutions has been associated with a significant reduction of AKI incidence and mortality7-9. These findings have been further investigated by several randomized controlled trials (RCT).

In 2015, the SPLIT trial compared Plama-Lyte 148 to isotonic saline in a population of surgical patients (n = 2278), with low severity (mean SAPS 2 score in both groups = 14.1)10. This trial did not show any difference for the risk of AKI (Primary outcome) or secondary classical outcomes (28-day and hospital mortality, use of renal replacement therapy). In this study, patients received a mean fluid volume of 1,700 mL during the first 24 hours after inclusion. In the 24 hours prior to inclusion, 60% of included patients in both groups received about 1,000 mL of balanced fluid. The chloride concentration was not reported.

In 2018, the SMART trial included 15,802 medical and surgical ICU patients and compared prognosis according to the use of balanced fluids (lactated Ringer’s or Plasma-Lyte A solutions) vs isotonic saline for fluid administration. This large pragmatic, cluster-randomized, multiple-crossover trial conducted in 5 ICUs of an academic center showed a significant reduction of Major Adverse Kidney Event (the composite of death, need of renal replacement therapy or worsened kidney function) within 30 days (MAKE-30, primary outcome) in the balanced-solutions group11. Even significant, the difference was modest as the use of balanced solutions rather than isotonic saline only prevented 1 ICU patient among 94 from new renal-replacement therapy or persistent renal dysfunction or death at day 3011. A secondary analysis of SMART trial results showed that the use of balanced crystalloids was associated with significant lower mortality12. In SMART trial, the median infused volume from day 1 to 3 was 1,000 mL [0 – 2,900 mL] and the mean infused volume was 1,900 ml (+/- 2,800 mL) in both groups. In the balanced-crystalloids group, fewer patients had a measured plasma chloride concentration greater than 110 mmol per liter as compared to saline group (24.5% vs. 35.6%, p < 0.001). The incidence of severe acidosis (plasma bicarbonate concentration < 20 mmol/L) was also significantly reduced in the balanced group. The same research group published at the same time a similar randomized study (SALT-ED trial) in a less-severe emergency department population (n = 13,347). This trial did not show any difference in hospital free-days (primary outcome) between the 2 types of fluids, but the use of balanced crystalloids was associated with a significant reduction of MAKE-30 (secondary outcome)13.

In 2021, the BaSICS trial compared the 2 types of fluids in 10,520 analyzed ICU patients, in whom 48% were included after planned surgery14. Both groups received a median fluid volume of 1,500 mL in the first 24 hours after inclusion. The 90-days mortality (primary outcome) was not statistically different and no difference in renal function was reported (secondary outcome). The only significant result was a mortality increase with balanced fluids in the subgroup of traumatic brain injury14.

The PLUS trial has just been published on January 2022 in the New England Journal of Medicine (NEJM)15. This trial initially planned to include 8,800 patients (From 53 Australian and New Zealand ICU’s) to detect an absolute difference of 2.9 % in 90-day all-cause mortality from an estimated baseline mortality of 23%, with a 90% power. Patients were assigned to receive either Plasma Lyte 148 or isotonic saline. Because of COVID 19 pandemic, study recruitment was stopped in December 2020 and a new sample calculation showed that 5,000 analyzed patients were needed to show a mortality difference of 3.8%, with a 90 % power, on the basis of the same baseline mortality. The trial included 5,037 patients and 4,844 were finally analyzed for the primary outcome (45 % surgical patients). The median APACHE 2 score was 19 in the 2 groups. In both groups, 55% of patients of saline group received at least 500 mL of balanced solution in the 24 hours before inclusion and conversely for the balanced group. During the first 24 hours after randomization, patients received a mean fluid volume of about 1,500 mL in both groups.

At inclusion, in both groups, serum chloride was slightly elevated, 105.5 (+/- 6) mmol/L and similar in both groups. In the days following randomization, in the saline group, pH was significantly lower from day 1 to day 4 while chloride concentration was significantly higher from day 2 to day 7 (maximal value 108 mmol/l, absolute difference between the 2 groups = 1.99 (1.76 to 2.21)). This was consistent with results of SMART trial. However, in contrast with SMART trial results, no patient reached a serum chloride level of 110 mmol/l.

As a main result, no difference in 90 days mortality rate (primary objective) was observed between the 2 groups. The mortality rate was consistent with the study hypothesis: 21.8% in balanced group and 22% in saline group. Moreover, no difference was observed for new renal-replacement therapy or maximal increase in serum creatinine level (secondary objectives). The median fluid volume administered in the first 24 hours was about 1,500 mL in both group with no statistical difference.

The PLUS trial results are in accordance with those of SPLIT10 and BaSICS trials14, that do not suggest a difference between the 2 types of fluids. They are inconsistent with those of SMART and SALT-ED trials that suggests a slight but significant higher AKI-associated risk with saline use11,13. These discrepancies can probably be explained by the different numbers of needed subjects (higher in SMART and SALT-ED trials) and different primary endpoints: 90 days mortality in PLUS and BaSICS, trials AKI stage 2 risk for SPLIT trial, MAKE-30 for SMART trial, Hospital free-days for SALT-ED trial. It could be hypothesized that a composite score as MAKE 30 could be a better way to detect AKI risk than mortality or need for renal replacement therapy. This point needs to be clarified in future trials. Moreover, the deleterious renal effects observed in SMART trial can also be associated with higher proportion of patients with a serum chloride concentration > 110 mmol/L, which has not been reported in other trials. This suggests a potential prognosis value of serum chloride concentration, easily available at bedside.

Interestingly, the authors of PLUS trial performed a meta-analysis published in NEJM *evidence*, a new journal added to the NEJM group in 202216,17. This study analyzed data from 6 RCTs and concluded that the use of balanced crystalloids seems to be associated with a maximal mortality decrease of 9 % in ICU patients17.

Finally, there is a common point in PLUS, BaSICS, SMART, SALT-Ed and SPLIT trials: the total median fluid infused volume during the first 24 hours ranges from 1,000 to 2,000 mL. A pragmatic message could be that, for such infused volume, the risk of poor outcome with saline use is either absent or low. Conversely, the use of larger saline volume seems hazardous. Furthermore, while there are trials showing benefits to using balanced fluids, there are no studies showing a benefit for using saline, at best it is equivalent.

To settle this question definitively, it will probably be necessary in the future to envisage more "physiological" studies, where the fluids will be chosen according to the patient's ionogram and more specifically his chloremia. Another solution could also be to use bicarbonate fluids, such as renal replacement fluids, which are even more physiological than balanced ones, but manufacturers would have to be able to produce them in smaller (currently 5 liters) and less expensive containers.

**References:**

1. Evans G: The abuse of normal salt solution. JAMA 1911; 57: 2126-7

2. Scheingraber S, Rehm M, Sehmisch C, Finsterer U: Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 1999; 90: 1265-70

3. Chowdhury AH, Cox EF, Francis ST, Lobo DN: A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte(R) 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg 2012; 256: 18-24

4. Chowdhury AH, Cox EF, Francis ST, Lobo DN: A randomized, controlled, double-blind crossover study on the effects of 1-L infusions of 6% hydroxyethyl starch suspended in 0.9% saline (voluven) and a balanced solution (Plasma Volume Redibag) on blood volume, renal blood flow velocity, and renal cortical tissue perfusion in healthy volunteers. Ann Surg 2014; 259: 881-7

5. Ronco C, Bellomo R, Kellum JA: Acute kidney injury. Lancet 2019; 394: 1949-1964

6. Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders HJ: Acute kidney injury. Nat Rev Dis Primers 2021; 7: 52

7. Zampieri FG, Ranzani OT, Azevedo LC, Martins ID, Kellum JA, Liborio AB: Lactated Ringer Is Associated With Reduced Mortality and Less Acute Kidney Injury in Critically Ill Patients: A Retrospective Cohort Analysis. Crit Care Med 2016; 44: 2163-2170

8. Raghunathan K, Bonavia A, Nathanson BH, Beadles CA, Shaw AD, Brookhart MA, Miller TE, Lindenauer PK: Association between Initial Fluid Choice and Subsequent In-hospital Mortality during the Resuscitation of Adults with Septic Shock. Anesthesiology 2015; 123: 1385-93

9. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M: Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA 2012; 308: 1566-72

10. Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, McGuinness S, Mehrtens J, Myburgh J, Psirides A, Reddy S, Bellomo R, Investigators S, Anzics CTG: Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial. JAMA 2015; 314: 1701-10

11. Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, Stollings JL, Kumar AB, Hughes CG, Hernandez A, Guillamondegui OD, May AK, Weavind L, Casey JD, Siew ED, Shaw AD, Bernard GR, Rice TW, Investigators S, the Pragmatic Critical Care Research G: Balanced Crystalloids versus Saline in Critically Ill Adults. N Engl J Med 2018; 378: 829-839

12. Brown RM, Wang L, Coston TD, Krishnan NI, Casey JD, Wanderer JP, Ehrenfeld JM, Byrne DW, Stollings JL, Siew ED, Bernard GR, Self WH, Rice TW, Semler MW: Balanced Crystalloids versus Saline in Sepsis. A Secondary Analysis of the SMART Clinical Trial. Am J Respir Crit Care Med 2019; 200: 1487-1495

13. Self WH, Semler MW, Wanderer JP, Wang L, Byrne DW, Collins SP, Slovis CM, Lindsell CJ, Ehrenfeld JM, Siew ED, Shaw AD, Bernard GR, Rice TW, Investigators S-E: Balanced Crystalloids versus Saline in Noncritically Ill Adults. N Engl J Med 2018; 378: 819-828

14. Zampieri FG, Machado FR, Biondi RS, Freitas FGR, Veiga VC, Figueiredo RC, Lovato WJ, Amendola CP, Serpa-Neto A, Paranhos JLR, Guedes MAV, Lucio EA, Oliveira-Junior LC, Lisboa TC, Lacerda FH, Maia IS, Grion CMC, Assuncao MSC, Manoel ALO, Silva-Junior JM, Duarte P, Soares RM, Miranda TA, de Lima LM, Gurgel RM, Paisani DM, Correa TD, Azevedo LCP, Kellum JA, Damiani LP, Brandao da Silva N, Cavalcanti AB, Ba Si, the Bm: Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients: The BaSICS Randomized Clinical Trial. JAMA 2021

15. Finfer S, Micallef S, Hammond N, Navarra L, Bellomo R, Billot L, Delaney A, Gallagher M, Gattas D, Li Q, Mackle D, Mysore J, Saxena M, Taylor C, Young P, Myburgh J, Investigators PS, the A, New Zealand Intensive Care Society Clinical Trials G, Investigators PS, Australian New Zealand Intensive Care Society Clinical Trials G: Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults. N Engl J Med 2022; 386: 815-826

16. Sacks CA, Hardin CC, Normand SL, Kadire S, Takvorian K, Galloway N, Linga R, Hannon P, Drazen J, Rubin E: NEJM Evidence - A New Journal in the NEJM Group Family. N Engl J Med 2022; 386: 182-183

17. Hammond N ZG, Di Tanna GL et al: Balanced crystalloids versus saline in critically ill adults — a systematic review with meta-analysis. NEJM Evidence 2022