COMMENTARY

Is SOLUTE the Solution to Which Solution (to Use)?

Atul P Kulkarni[1,2], Ruchira W Khasne[3]

Received on: 21 November 2024; *Accepted on:* 21 November 2024; *Published on:* 30 November 2024

Keywords: Acute kidney injury, Balanced salt solutions, Renal replacement therapy, Ringer lactate, Normal saline.
Indian Journal of Critical Care Medicine (2024): 10.5005/jp-journals-10071-24867

[1]Department of Anesthesiology, Division of Critical Care Medicine, Critical Care, Tata Memorial Hospital, Mumbai, Maharashtra, India

[2]Homi Bhabha National Institute, Mumbai, Maharashtra, India

[3]Department of Anaesthesiology, SMBT Institute of Medical Sciences and Research Center, Nashik, Maharashtra, India

Corresponding Author: Atul P Kulkarni, Department of Anesthesiology, Division of Critical Care Medicine, Critical Care, Tata Memorial Hospital; Homi Bhabha National Institute, Mumbai, Maharashtra, India, Phone: +91 9137657036, e-mail: kaivalyaak@yahoo.co.in

How to cite this article: Kulkarni AP, Khasne RW. Is SOLUTE the Solution to Which Solution (to Use)? Indian J Crit Care Med 2024;28(12): 1096–1100.

Source of support: Nil

Conflict of interest: Dr Atul P Kulkarni is associated as the Editor-in-Chief of this journal and this manuscript was subjected to this journal's standard review procedures, with this peer review handled independently of the Editor-in-Chief and his research group.

The commonest crystalloid used in many ICUs, Normal saline (NS), contains much higher concentrations of both sodium and chloride (154 mmol/L each) compared with human plasma. Electrolyte imbalance can affect various organ systems, in particular the heart, brain, and kidney, almost immediately. Sydney Ringer investigated the effects of different ions on contractility of the heart, and found that both calcium and potassium were necessary for restoring the contractility of the heart.[1,2] He went on to formulate the Ringer's lactate solution. In 1930s, Alexis Frank Hartmann found that trying to counteract the uncompensated metabolic acidosis with rapid injection of sodium bicarbonate pushed the plasma milieu into uncompensated metabolic alkalosis, and he therefore substituted the bicarbonate with sodium lactate.[3,4] This is a nearly iso-osmolar solution (273 mOsm) solution and has a balanced mixture of electrolytes nearly similar to plasma. Since then, many multielectrolyte solutions have become available for clinical use (Table 1).

Scheingraber et al., first reported the occurrence of hyperchloremic metabolic acidosis in patients receiving NS (but not in those receiving Ringers lactate: RL) undergoing gynecologic surgeries.[5] It is surprising to note that the patients received over 6,000 mL fluid over a period of little over 2 h. There was a significant drop in pH, bicarbonate levels (5 mmol/L), and base excess (–10 mmol/L) in the patients receiving NS. While we do not know what was the final outcome of these patients, it is now very obvious that way too much volume was given to these patients. This acidosis was the result of a decrease in the strong anion gap induced by high plasma levels of chloride and excessive renal elimination of bicarbonates.

It is now evident that infusion of excessive volumes of NS saline will lead to hyperchloremic acidosis. The important question is whether this causes an increase in mortality. Gunnerson et al., classified 845 patients (with standard base excess ≤-2 mEq/L) into various types of acidosis.[6] The patients with hyperlactatemia and raised strong ion gap (SIG) had an increased mortality (56 and 39% respectively), while the patients with hyperchloremic acidosis (29%) had mortality similar to those without acidosis (26%). This is unfortunately only such study.

For ascribing therapeutic benefit or harm to any intervention, three criteria need to be fulfilled: biological plausibility, experimental animal data, and reasonable clinical evidence. In an elegant study, Wilcox demonstrated in denervated kidneys that infusion of solutions with high chloride content progressively increased renal

Table 1: Electrolyte contents of plasma and various crystalloids

Solution	*Sodium*	*Potassium*	*Calcium*	*Magnesium*	*Chloride*	*Acetate*	*Gluconate*	*Malate*	*Lactate*	*Osmolarity (mOsm/L)*
Plasma	135–145	3.5–4.5	2.2–2.6	0.8–1.0	91–111	0.02–0.2	0	0	1–2	275–295
Ringer's lactate	130	4.0	2.5	0	109	0	0	0	28	273
Ringer's acetate	145	4.0	2.5	1.0	127	24	0	5	0	309
Hartmann's solution	131	5.4	1.8	0	112	0	0	0	28	280
Normal saline	154	0	0	0	154	0	0	0	0	308
Plasmalyte A	140	5.0	0	3.0	98	27	23	0	0	294
Normosol–R	140	5.0	0	3.0	98	27	23	0	0	295
Isolyte S	141	5.0	0	3.0	98	27	23	0	0	295
Isolyte P*	23	20	0	3.0	29	23	0	0	0	340
Isolyte M**	36	35	0	0	49	20	0	0	0	390

*Also contains phosphate 1.5 mmol/L; **Also contains phosphate 7.5 mmol/L; Isolyte P and Isolyte M are solutions in 5% dextrose

vasoconstriction and decreased glomerular filtration rate (GFR).[7] He also noted that this chloride load effect overrides the effect of osmolarity. The change in afferent lumen diameter is variable under the physiological conditions and is reduced maximally to eight times the normal size, when the chloride is in the range of 110–120 mmol/L.[8] Excessively high chloride loads have also been shown to produce histological changes in rat models of sepsis in the form of vacuolization, loss of brush border, and dilation of the tubular lumen.[9]

A before and after study comparing the effect of liberal to restricted chloride administration found that restriction of chloride-rich fluids led to a decreased incidence of acute kidney injury (AKI) and need for renal replacement therapy (RRT).[10] Since then, many studies have looked to answer whether the use of balanced salt solutions (BSS) in critically ill patients provides an advantage over the use of NS (Table 2).[11–15]

Contrary to currently available evidence, the recently published SOLUTE study found favorable effects of infusion of newer BSS in critically ill patients on outcomes such as AKI incidence, duration of mechanical ventilation and ICU and hospital length of stay, and ICU mortality, compared with infusion of NS mainly, but also over RL.[16] In this study, prospective observational cohort data were collected with a convenience sample of 2,452 patients. This study spanned over nearly 3 years, owing to the COVID-19 pandemic, and the patients with COVID-19 were excluded. The baseline APACHE II and sequential organ failure assessment (SOFA) scores across the groups suggest moderate-to-severe critical illness. Normal saline was the preferred fluid in most Indian ICUs, this is surprising considering nearly 80% of data came from ICUs in private hospitals, since the most common consideration while choosing the intravenous fluid is economic: BSS which are much costlier than NS or RL are most likely to be used in private hospitals.

The study collected the data about the type of fluid used and the incidence of AKI over the first 3 days of ICU stay. From a similar baseline mean serum creatinine which itself was higher than the normal range, a large proportion of patients across all three groups developed AKI on the first day itself, the incidence being much higher in the NS group (37% NS vs 16% RL vs 18%). This is hard to explain only on the basis of fluids received on one day. In fact, the incidence of AKI seems to come down on two subsequent days in the NS and BSS groups and marginally goes up in the RL group. We do not have information about the total amount of fluids received in each group and do not have Cl^- measurements on any of the days. A large excessive chloride load has to be presented to the kidneys for causing renal vasoconstriction, leading to reduced blood flow and thus reduced GFR. This means the rapid infusion of large volumes of NS over a short period of time. Whether this happened in the NS group is difficult to ascertain as we do not have the information about the volume infused. The daily fluid balance seems to be least in the BSS, then RL and NS groups, but again the patients do not seem to have excessively high positive fluid balance. Development of AKI per se is not a problem, but the need for RRT is in that it adds to the costs and also to the increased length of the stay (LOS) in the ICU as well as the hospital. Renal replacement therapy was required only in a small proportion of the patients in each group and was similar in all groups. The reasons for longer ICU and hospital LOS in patients who received NS is a matter of conjecture. There were no guidelines for discharge, and each unit followed its own policy. We can presume a reluctance on the part of clinicians to discharge a patient with AKI. We do not have data about the number of patients with persistent

Table 2: Studies comparing normal saline vs balanced salt solutions[11–15]

Study	*Groups*	*Results*	*Interpretation*	*Implications*
SPLIT trial[11] 2,278 patients admitted to four ICUs in New Zealand	Cluster randomized double-blinded, crossover trial Intervention plasma-lyte 148: 1162 pts Control NS 1116 pts	Primary outcome: Proportion of patients with AKI based on RIFLE criteria within 90 days: No difference No statistical difference in any of the following: Incidence of AKI, need for RRT, mechanical ventilation, ICU readmission, length of stay All-cause and cause-specific mortality: 9.6% in the intervention group vs 9.2% in control group; $p = 0.77$	There was no difference in the AKI or requirement for RRT and no difference in hospital mortality (plasma-lyte-148 vs saline, 7.5% vs 8.6%, RR 0.87, 95% CI: 0.66–1.55, $p = 0.36$)	In this pilot study high proportion of elective surgical patients and relatively small volumes of study fluids were used The use of a buffered crystalloid compared with 0.9% sodium chloride did not reduce the risk of AKI
SMART[12] Single-center $n = 15,802$	Open-label, multiple-cluster, crossover RCT single-center trial. Compared buffered crystalloid (plasma-lyte A or RL) vs NS BSS: 7942 NS:7860	Major adverse kidney events (MAKE, a composite of death, dialysis, or doubling of baseline creatinine concentration) censored at 30 days: MAKE30 Primary outcome MAKE 30: significantly greater in NS group (MAKE 30; Balanced crystalloid group = 14.3%, saline group = 15.4%) (Marginal OR, 0.91; 95% CI: 0.84–0.99. Conditional OR, 0.90; 95% CI, 0.82–0.99; $p = 0.04$) Secondary outcomes: BSS vs NS	SMART trial favors administering intravenous BSS over NS to decrease a composite outcome of death, new RRT, or persistent renal dysfunction at 30 days	This is a large and strong methodological study adds further doubt to the safety of NS The composite endpoint is difficult to interpret and may exaggerate the benefit of BSS

(Contd...)

Table 2: *(Contd...)*

Study	*Groups*	*Results*	*Interpretation*	*Implications*
		Death; before discharge or at day 30: 10.3% vs 11.1% $p = 0.06$ Receipt of new RRT: 2.5% vs 2.9% $p = 0.08$ Persistent renal dysfunction: 6.4% vs 6.6% $p = 0.60$ No difference in ICU-free days, ventilator-free days, vasopressor-free days, Stage II (or higher) AKI developing after enrolment Subgroup of patients with sepsis, in-hospital mortality was 25.2% in the balanced crystalloid group vs 29.4% in the saline group (adjusted OR 0.80; 95% CI, 0.67–0.97, $p = 0.02$)		
SALT-ED[13] BSS vs NS in noncritically ill adults in the emergency department $n = 13,347$	Open-label, multiple-cluster cross-over single-center randomized trial. Buffered crystalloid (Plasma-Lyte A or RL) vs NS	Primary outcome: No difference in the number of hospital-free days (median, 25 days in each group; adjusted OR BSS, 0.98; 95% [CI], 0.92–1.04; $p = 0.41$) Secondary outcomes: Patients in the BSS group had a significantly lower incidence of MAKE within 30 days (MAKE 30) than those in the NS group (4.7% vs 5.6%; adjusted odds ratio, 0.82; 95% CI, 0.70 to 0.95; $p = 0.01$) In-hospital death: No significant difference 1.4% in BSS vs 1.6% in NS group ($p = 0.36$)	No difference in hospital-free days BUT lower incidence of MAKE30 in the buffered balanced crystalloids group	Study in noncritically ill patients Adverse kidney events are less common with BSS The results from this study need to be replicated in a multicenter randomized controlled trial before any conclusions
The BaSICS[14] 75 ICUs in Brazil ($n = 11,000$)	Comparison between BSS and NS NS group 5,290 BSS group: 5,230	Primary outcome: No significant difference in 90-day mortality BSS 1381 of 5230 pts (26.4%) vs 1439 of 5290 patients (27.2%) NS (adjusted HR, 0.97 [95% CI, 0.90–1.05]; $p = 0.47$) No statistical difference in secondary outcomes incidence of AKI with the need for RRT within 90 days per 1,000 patient days No significant difference in 90-day mortality in rapid vs slow administration of fluid challenges In the slower infusion group, 1,406 of 5,276 patients (26.6%) had died by day 90 compared with 1414 of 5,244 patients (27.0%) in the control group	Use of a BSS compared with NS and the use of slower infusion rates as fluid bolus is compared with a faster rate of infusion did not reduce 90-day mortality	This is a large multicenter trial which showed the use of 0.9% NS appears safe But balanced crystalloid should be preferred for those patients who are acutely unwell with an unplanned ICU admission

(Contd...)

Table 2: *(Contd...)*

Study	*Groups*	*Results*	*Interpretation*	*Implications*
PLUS study[15] 53 ICUs in Australia and New Zealand *n* = 5,037	Double-blind, parallel-group, RCT BMES: 2,515 NS: 2,522	Primary outcome: Unadjusted 90-day mortality (BMES vs NS) 21.8% vs 22.0% (530 deaths in each group) ARR –0.15% (95% CI: –3.6–3.3) Secondary analysis: Showed no change in primary outcome when those receiving >500 mL of alternate fluid either prior to randomization or in the ICU post-randomization were excluded Post hoc analysis which aimed to account for those in BMES group who received open-label saline also showed no difference in the primary outcome Secondary outcomes: No significant difference in: New RRT, use of vasoactive drugs Days alive and free of mechanical ventilation, maximum creatinine level or increase in creatinine	The use of PL-148 compared with NS does not reduce 90-day all-cause mortality or risk of AKI	This high-quality, large RCT showed that NS does not reduce 90-day all-cause mortality or risk of AKI It provides no evidence that 0.9% sodium chloride causes harm

RIFLE, risk, injury, failure criteria

renal dysfunction or dialysis dependence, which may often lead to increased LOS. Even more difficult to surmise are the reasons for significantly higher mortality in the NS group compared with BSS group, while it was not different in the BSS and RL group. Since we do not have a formal sample size calculation, it is difficult to evaluate whether the study was powered for showing a mortality difference. A large retrospective study of over 1,00,000 patients looked at the variation in chloride concentration, total amount of chloride load administered (also adjusted for volume administered) and mortality. Mortality was lowest when the rise in chloride levels was minimal (0–10 mmol/L) or lower amounts of chloride (100–200 mmol/L) were administered.[17] This remained true even after adjustment was made for severity of illness and total volume. It therefore would have been useful to know the chloride levels or total chloride infused in the current study. Without this, it is difficult to attribute the increased mortality to the use of NS alone.

While it remains true from the physiological perspective that infusion of large volumes of NS is best avoided as it presents excessive chloride load, and may be associated with decreased GFR, the randomized controlled trials (RCTs) published so far have failed to show that it leads to increased incidence of AKI, need for RRT or an increase in mortality.

The SOLUTE study confirms that NS remains the most commonly used crystalloid in Indian ICUs. It appears that BSS have a better renal safety profile than NS, the practice in Indian ICUs probably needs to change toward using RL, considering the cost of the newer BSS. Normal saline is best reserved for situations in which it is indicated specifically such as treatment of symptomatic hyponatremia and traumatic brain injury (with monitoring of serum chloride concentration). In all other patients, RL or if your patients can afford it, newer BSS should be preferably used till we get evidence to the contrary. We just need to remember what George H Evans said about the harm meted out to the patients through the abuse of normal salt solution (sic).[18]

"One cannot fail to be impressed with the danger of such procedure, if one observes the utter recklessness with which salt solution is frequently prescribed…."

And

"In which the disastrous rôle played by the salt solution is lost sight of in the light of the serious condition which called forth its use; thus fatal results are undoubtedly frequently attributed to the pathologic condition".

Orcid

Atul P Kulkarni https://orcid.org/0000-0002-5172-7619
Ruchira W Khasne https://orcid.org/0000-0002-2322-6569

References

1. Ringer S. Concerning the influence exerted by each of the constituents of the blood on the contraction of the ventricle. J Physiol 1882;5–6 (3):380–393. DOI: 10.1113/jphysiol.1882.sp000111.
2. Ringer S. A further contribution regarding the influence of the different constituents of the blood on the contraction of the heart. J Physiol 1883;4(1):29–42. DOI: 10.1113/jphysiol.1883.sp000120.
3. Hartmann AF, Senn MJ. Studies in the metabolism of sodium r-lactate. I. Response of normal human subjects to the intravenous injection of sodiUM r-lactate. J Clin Invest 1932;11(2):327–335. DOI: 10.1172/JCI100414.
4. Hartmann AF, Senn MJ. Studies in the metabolism of sodium r-lactate. II. Response of human subjects with acidosis to the intravenous

injection of sodium r-lactate. J Clin Invest 1932;11(2):337–344. DOI: 10.1172/JCI100415.
5. Scheingraber S, Rehm M, Sehmisch, Finsterer U. Rapid saline infusion produces hyprchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 1999;90:1265–1270. DOI: 10.1097/00000542-199905000-00007.
6. Gunnerson KJ, Saul M, He S, Kellum JA. Lactate versus non-lactate metabolic acidosis: A retrospective outcome evaluation of critically ill patients. Crit Care 2006;10(1):R22. DOI: 10.1186/cc3987.
7. Wilcox CS. Regulation of renal blood flow by plasma chloride. J Clin Invest 1983; 71(3):726–735. DOI: 10.1172/jci110820.
8. Hansen PB, Jensen BL, Skott O. Chloride regulates afferent arteriolar contraction in response to depolarization. Hypertension 1998;32(6):1066–1070. DOI: 10.1161/01.hyp.32.6.1066.
9. Zhou F, Peng ZY, Bishop JV, Cove ME, Singbartl K, Kellum JA. Effects of fluid resuscitation with 0.9% saline versus a balanced electrolyte solution on acute kidney injury in a rat model of sepsis. Crit Care Med 2014; 42(4): e270–e278. DOI: 10.1097/CCM.0000000000000145.
10. 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(15):1566–1572. DOI: 10.1001/jama.2012.13356.
11. Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, et al. SPLIT Investigators; 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(16):1701–1710. DOI: 10.1001/jama.2015.12334.
12. Semler MW, Wanderer JP, Ehrenfeld JM, Stollings JL, Self WH, Siew ED, et al. SALT Investigators * and the Pragmatic Critical Care Research Group; SALT Investigators. Balanced crystalloids versus saline in the intensive care unit. The SALT randomized trial. Am J Respir Crit Care Med 2017;195(10):1362–1372. DOI: 10.1164/rccm.201607-1345OC.
13. Self WH, Semler MW, Wanderer JP, Wang L, Byrne DW, Collins SP, et al. SALT-ED Investigators. Balanced crystalloids versus saline in noncritically ill adults. N Engl J Med 2018;378(9):819–828. DOI: 10.1056/NEJMoa1711586.
14. Zampieri FG, Machado FR, Biondi RS, Freitas FGR, Veiga VC, Figueiredo RC, et al. 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;326(9):1–12. DOI: 10.1001/jama.2021.11684.
15. Finfer S, Micallef S, Hammond N, Navarra L, Bellomo R, Billot L, et al. Balanced multielectrolyte solution versus saline in critically ill adults. N Engl J Med 2022;386(9):815–826. DOI: 10.1056/NEJMoa2114464.
16. Gupta S, Dixit S, Tomar DS, Zirpe K, Govil D, Choudhry D, et al. Salt based or BaLanced SolUtion–trends existing in Indian intensive care units: a multicenter prospective observational cohort study (SOLUTE Study). Indian J Crit Care Med 2024;28(11):1028–1037. DOI: 10.5005/jp-journals-10071-24825.
17. Shaw AD, Raghunathan K, Peyerl FW, Munson SH, Paluszkiewicz SM, Schermer CR. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. Intensive Care Med 2014; 40(12):1897–1905. DOI: 10.1007/s00134-014-3505-3.
18. Current Comment. JAMA 1912; LIX (14):1297–1299. DOI: 10.1001/jama.1912.04270100065028.