Balanced Crystalloid Solutions

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Abstract

Intravenous fluid therapy is the most common intervention received by acutely ill patients. Historically, saline (0.9% sodium chloride) has been the most frequently administered intravenous fluid, especially in North America. Balanced crystalloid solutions (e.g., lactated Ringer's, Plasma-Lyte) are an increasingly used alternative to saline. Balanced crystalloids have a sodium, potassium, and chloride content closer to that of extracellular fluid and, when given intravenously, have fewer adverse effects on acid–base balance. Preclinical research has demonstrated that saline may cause hyperchloremic metabolic acidosis, inflammation, hypotension, acute kidney injury, and death. Studies of patients and healthy human volunteers suggest that even relatively small volumes of saline may exert physiological effects. Randomized trials in the operating room have demonstrated that using balanced crystalloids rather than saline prevents the development of hyperchloremic metabolic acidosis and may reduce the need for vasopressors. Observational studies among critically ill adults have associated receipt of balanced crystalloids with lower rates of complications, including acute kidney injury and death. Most recently, large randomized trials among critically ill adults have examined whether balanced crystalloids result in less death or severe renal dysfunction than saline. Although some of these trials are still ongoing, a growing body of evidence raises fundamental concerns regarding saline as the primary intravenous crystalloid for critically ill adults and highlights fundamental unanswered questions for future research about fluid therapy in critical illness.

Keywords: intravenous fluid; saline; balanced crystalloids; acute kidney injury; critical illness

Intravenous fluid therapy has been fundamental to acute care for more than a century (1). Each year, more than 30 million patients receive intravenous fluid for resuscitation or maintenance of intravascular volume or as a medication carrier (2). Crystalloid solutions are the most commonly administered intravenous fluid and are composed of electrolytes in water that cross easily from the vascular space into the interstitium (3). Two basic classes of crystalloid are available to clinicians: saline (0.9% sodium chloride) and balanced crystalloids (e.g., lactated Ringer's, Plasma-Lyte A [Baxter Healthcare]). Although saline has been the predominantly used crystalloid in North America and in many other parts of the world (4), recent evidence from basic science research, observational research, and clinical trials suggests that using balanced crystalloids rather than saline may have beneficial effects on acid–base balance, renal physiology, and patient outcomes.

Crystalloid Solutions

Saline (a/k/a 0.9% sodium chloride or "normal saline") contains 154 mmol/L of both sodium and chloride (Table 1). Balanced crystalloids (a/k/a "buffered crystalloids") are solutions in which chloride anions are replaced with bicarbonate or buffers to reduce the perturbations in acid–base balance resulting from fluid administration (Figure 1) (5). The original balanced crystalloids achieved this by replacing chloride anions with bicarbonate anions (1). Because of the instability of bicarbonate-containing solutions in standard gas-permeable bags, modern balanced crystalloids contain alternative anions, such as lactate, acetate, and gluconate, that are rapidly metabolized or excreted (6).

Preclinical Research

Both balanced crystalloids and saline have been available for clinical use and scientific examination for more than 100 years. Concerns about the effects of saline's

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Table 1. Composition of Crystalloid Solutions

Fluid	Sodium	Potassium	Calcium	Magnesium	Chloride	Acetate	Gluconate	Malate	Lactate	Osmolarity
Plasma	135–145	4.5–5.0	2.2–2.6	0.8–1.0	94–111	0.02–0.2			1–2	275–295
Plasma-Lyte A	140	5.0		3.0	98	27	23			294
Normosol-R	140	5.0		3.0	98	27	23			295
Isolyte S	141	5.0		3.0	98	27	23			295
Ringer's acetate	145	4.0	2.5	1.0	127	24		5		309
Lactated Ringer's	130	4.0	2.7		109				28	273
Hartmann's solution	131	5.4	1.8		112				28	280
0.9% sodium chloride	154				154					308

All values are in mEq/L, except calculated osmolarity, which is in mOsm/L. Plasma-Lyte A is "Multiple Electrolyte Injection, Type 1, USP," from Baxter Healthcare Corporation; Normosol-R is "Multiple Electrolyte Injection, Type 1, USP," from Hospira, Inc.; Isolyte S is from B. Braun Medical Inc.; Ringer's acetate is "Sterofundin ISO, Isotonic Electrolyte Solution," from B. Braun; lactated Ringer's is "lactated Ringer's Injection, USP," from Baxter Healthcare Corporation; Hartmann's solution is "Compound Sodium Lactate" from Baxter Healthcare Corporation; and 0.9% saline is "Sodium Chloride Injection, USP," from Baxter Healthcare Corporation.

composition were first raised at the turn of the 20th century, when researchers noted that saline did not maintain electrical or mechanical activity of isolated muscle preparations. In 1901, Harvey Cushing declared saline to be "poisonous" (7). Despite the concerns, in the first three decades of the 20th century, saline went from a fluid developed for laboratory use to the most common fluid administered to patients globally. By the 1940s, saline was so ubiquitous in clinical practice that when acidosis resulting from fluid resuscitation was first observed, it was mistakenly attributed to dilution of bicarbonate (8) rather than to saline. After the introduction of standard base excess in the 1970s (9) and strong ion difference in the 1980s (10), quantitative analyses made it apparent that chloride concentration was an important contributor to acid–base derangements in critical illness.

Acid–Base Balance

In 1998, Kellum and colleagues first quantified the effect of saline on acid–base balance (11). Among endotoxemic dogs resuscitated with saline, changes in strong ion difference demonstrated that saline alone accounted for more than one-third of the overall acidosis. Subsequent work in the same laboratory identified the supraphysiologic chloride content of saline as a potential regulator of acid–base physiology and clinical outcomes (12).

Despite the consistently observed relationship between intravenous saline resuscitation and hyperchloremic metabolic acidosis, uncertainty remained about whether, and how, saline-induced acidosis might affect organ function and survival. Observations of the clinical effects of acidosis from the field of exercise physiology suggested even profound metabolic acidosis (arterial blood pH <7.0) generated by vigorous exercise was well tolerated and without lasting effects on organ function (13, 14). Similarly, permissive hypercapnia for patients with acute respiratory distress syndrome produced moderate to severe acidosis without negative effects on organ function or survival (15). Indeed, healthy humans and animals appear to be able to tolerate rather significant acidosis, at least for short periods. In the context of critical illness, however, acidosis appears to have meaningful detrimental effects on the vasculature (16). Acidosis induces vasodilation (17), which may be beneficial in exercise but may worsen shock. In rats, after cecal ligation and puncture, even modest acidosis (standard base excess of -5 to -10 mEq/L) induced by infusion of dilute hydrochloric acid, decreases blood pressure (18) in a dose–response fashion. These hemodynamic effects take up to 8 hours to fully develop and are not completely explained by changes in plasma nitrate/nitrite concentrations. The concept that resuscitation with saline-containing fluids induces acidosis that can contribute to cardiovascular collapse provides a potential mechanism for the findings of several recent randomized trials examining fluid resuscitation for acutely ill patients (19–21).

Inflammation

Saline-induced hyperchloremic metabolic acidosis also appears to induce inflammation in cell culture and animal models. Macrophage-like RAW 264.7 cells incubated with LPS and a pH of 7.0 exhibit increased nuclear factor-κB DNA binding when acidosis is induced with hydrochloric acid, but not when acidosis is induced with lactic acid (22). Studies demonstrating antiinflammatory effects of CO_2 (23) suggest that acidosis may have variable effects on the inflammatory response, depending on the acid involved, and highlight important differences between endogenous acids such as lactate and CO_2 and hyperchloremic acidosis, which is often iatrogenic.

Among rats made septic by cecal ligation and puncture, saline-treated animals experienced higher plasma IL-6 concentrations (24). These results are consistent with prior animal studies demonstrating increased cytokine expression with hydrochloric acid–induced hyperchloremic acidosis, even when blood pressure is maintained (25).

Renal Function

The effects of crystalloid solutions with high chloride content on the kidney have been equally controversial. A 1983 study of isolated, perfused greyhound kidneys found that increasing chloride concentration in the perfusate produced a progressive renal vasoconstriction and fall in glomerular filtration rate (26). These effects were independent of the renal nerves and appeared to be related to tubular chloride reabsorption (26). Subsequent studies among healthy human volunteers, discussed below, found similar decreases in renal blood flow velocity and perfusion with high-chloride solutions (27, 28).

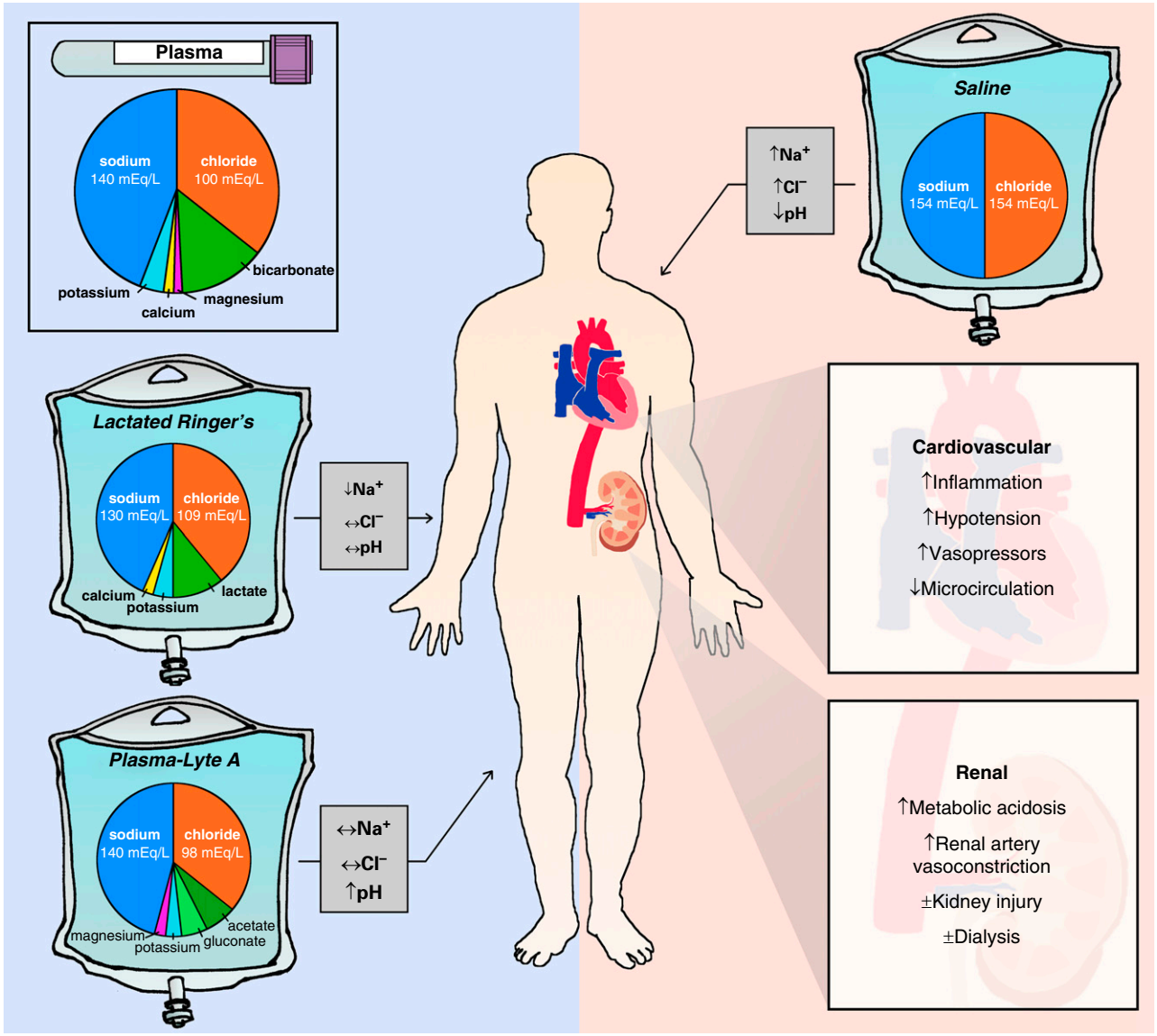

Figure 1. Effects of crystalloid composition on plasma electrolytes and organ function. The figure displays the electrolyte content of human plasma and of each intravenous crystalloid solution. Gray boxes indicate the expected effect of administration of each crystalloid on plasma electrolytes. Panels on the right summarize detrimental effects of saline-induced hyperchloremic metabolic acidosis on the cardiovascular and renal systems reported in preclinical and clinical research.

Healthy rats treated with intravenous saline did not develop kidney damage, but animals made septic with cecal ligation and puncture were a different story. Compared with Plasma-Lyte treatment, resuscitation with saline resulted in significantly worse kidney injury severity, as measured by RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) criteria (29). These results were consistent with kidney histology and biomarkers of acute kidney injury (24). Twenty-four-hour survival also favored Plasma-Lyte resuscitation (76.6% vs. 53.3%; $P = 0.03$).

Clinical Research

Building on a growing body of preclinical research, studies over the last three decades have compared balanced crystalloids with saline in controlled experiments among healthy volunteers, observational studies in acute illness, randomized trials in the operating room, and large randomized trials among critically ill adults.

Healthy Volunteers

Multiple randomized crossover trials have compared intravenous administration of high-chloride versus low-chloride solutions in healthy human volunteers (27, 28, 30). When healthy volunteers received 2 L of either saline or Plasma-Lyte over 1 hour, saline significantly decreased renal artery blood velocity, decreased renal cortical tissue perfusion, decreased urine output, and increased extravascular fluid accumulation compared with Plasma-Lyte (27). Similarly, when healthy volunteers received 1 L of intravenous 6% hydroxyethyl starch (HES) over 30 minutes, HES in saline decreased renal cortical perfusion compared with HES in balanced

crystalloid (28). These findings provide modest support for the idea that in humans, like in animal models (26), saline-induced hyperchloremia may cause increased tubuloglomerular feedback and decreased renal cortical perfusion.

Observational Studies

Much of the early interest in the potential effects of crystalloid composition on clinical outcomes for acutely ill adults arose from large observational studies in the operating room and ICU. A retrospective study of more than 30,000 major abdominal surgery patients drawn from the Premier Perspective Comparative Database found that after propensity score adjustment and matching, patients treated with balanced crystalloids experienced fewer complications and less renal failure requiring dialysis (31). A prospective observational study of 542 patients undergoing major surgery found that after adjusting for fluid balance and amount of fluid received, low-chloride solutions were independently associated with a lower risk of acute kidney injury than high-chloride solutions (32).

Three observational studies compared balanced crystalloids with saline among patients receiving fluid resuscitation for sepsis or septic shock (33–35). A retrospective analysis of more than 100,000 adults from a Cerner database meeting systemic inflammatory response criteria found that, after adjusting for the total volume of resuscitation fluid received, receipt of a larger chloride load was associated with increased odds of death (odds ratio, 1.09; 95% confidence interval [CI], 1.06–1.13) (33). A propensity-matched analysis of over 6,000 adults in a Premier database with a diagnosis of sepsis who received at least 2 L of intravenous fluid found that receipt of balanced crystalloids was associated with a 3.2% (95% CI, 1.5–5.0%) lower absolute risk of in-hospital mortality (relative risk, 0.86; 95% CI, 0.78–0.94) (34). Another analysis of a Premier database examining more than 60,000 patients with sepsis and receiving vasopressors also found that after propensity score matching, balanced crystalloids were associated with a lower risk of in-hospital mortality (risk ratio, 0.84; 95% CI, 0.76–0.92) (35). Yet another study found that among patients receiving large-volume resuscitation (>60 ml/kg in 24 h), chloride load was associated with decreased 1-year survival, even after controlling for total fluid volume, age, and baseline severity of illness (36).

Finally, a before-and-after study compared 760 patients admitted to a single ICU during a period in which high-chloride solutions (saline, 4% gelatin, 4% albumin) were used with 773 patients admitted to the same ICU during a period in which low-chloride solutions (Hartmann solution, Plasma-Lyte 148, 20% albumin) were used (37). Acute kidney injury (odds ratio, 0.52; 95% CI, 0.37–0.75) and receipt of renal replacement therapy (odds ratio, 0.52; 95% CI, 0.33–0.81) were less common during the low-chloride period. The odds ratio for mortality during the low-chloride period compared with the high-chloride period was 0.88 (95% CI, 0.66–1.18). A subsequent analysis, however, suggested that unidentified confounders (e.g., decreasing use of gelatins over time, Hawthorne effect) may have contributed to the observed differences in acute kidney injury and renal replacement therapy between the low-chloride and high-chloride periods (38).

Clinical Trials in the Operating Room

Numerous small clinical trials have compared balanced crystalloids with saline among patients undergoing renal and nonrenal surgery. Early trials comparing lactated Ringer's to saline among patients undergoing gynecologic surgery (39) or abdominal aortic aneurysm repair (40) found that saline resuscitation produced hyperchloremia, metabolic acidosis, and decreased strong ion difference. These findings were confirmed across multiple operative populations, including women undergoing cesarean section (41), adults undergoing neurosurgery (42–44), and adults undergoing major abdominal surgery (45). Balanced crystalloids also appeared to result in lower concentrations of biomarkers of early acute kidney injury (e.g., neutrophil gelatinase-associated lipocalin) among adults undergoing major abdominal surgery (45).

A recent, patient-level, double-blind, randomized trial compared an acetate-buffered balanced crystalloid with saline among patients undergoing major abdominal surgery (21). The trial was terminated after the enrollment of 60 of 240 planned patients, when, at the interim analysis, 97% of patients in the saline group met the primary outcome of requiring catecholamine infusion to maintain mean arterial pressure, compared with 67% in the balanced crystalloid group ($P = 0.03$). Patients randomized to the saline group experienced more frequent hyperchloremic metabolic acidosis, earlier and more frequent receipt of vasopressors, and higher overall doses of vasopressors, although early stopping of the trial for safety may overestimate the magnitude of these effects.

The LICRA (Limiting I.V. Chloride to Reduce AKI) study is the largest trial to date comparing balanced crystalloids with saline in the operating room. LICRA was a single-cluster, double-crossover trial comparing low-chloride solutions (balanced crystalloids or 20% albumin) with high-chloride solutions (saline or 4% albumin) among 1,136 adults undergoing cardiac surgery at a single academic center (46). Patients received nearly 5 L of study fluid, with a mean difference between groups in highest plasma chloride concentration of 4 mmol/L. The incidence of acute kidney injury was not significantly different between the balanced crystalloid (29.1%) and saline (33.3%) groups (odds ratio, 0.82; 95% CI, 0.64–1.05). Temporal changes over the course of the crossover study, however, resulted in imbalances between the study groups in baseline factors expected to modify the risk of acute kidney injury. Specifically, the balanced crystalloid and saline groups differed with regard to stage of chronic kidney disease at baseline, receipt of extracorporeal membrane oxygenation or a ventricular assist device, and intraoperative receipt of vancomycin, leaving residual uncertainty regarding the relative effects of balanced crystalloids and saline during cardiac surgery.

Patients undergoing renal transplant represent a unique population in which the potential effects of balanced crystalloids versus saline on acid–base status, plasma electrolyte concentrations, and renal function may be magnified. Seven randomized trials have compared balanced crystalloids with saline during renal transplant (47–53). All found that use of balanced crystalloids resulted in lower rates of hyperchloremic metabolic acidosis. Four found lower rates of hyperkalemia with balanced crystalloids than with saline (47–50), perhaps owing to saline-induced hyperchloremic acidosis shifting potassium out of cells into the extracellular fluid (54). The effect of crystalloid composition on renal allograft function after transplant and the effect of balanced crystalloids versus

saline on plasma potassium concentration among other patient populations remain unclear (55).

Clinical Trials in Acute Care

Two cluster-randomized cluster-crossover pilot trials compared balanced crystalloids with saline among adult ICU patients (56, 57). The SPLIT (0.9% Saline versus Plasma-Lyte 148 for ICU fluid Therapy) trial compared Plasma-Lyte 148 with 0.9% sodium chloride among 2,278 patients admitted to four ICUs in New Zealand (56). Patients were predominantly admitted after cardiovascular surgery, were at low risk of death by baseline Acute Physiologic Assessment and Chronic Health Evaluation score, received primarily balanced crystalloid before ICU admission, and received a median of 2.0 L of isotonic crystalloid after enrollment. The relative risk of in-hospital mortality with balanced crystalloids compared with saline was 0.87 (95% CI, 0.64–1.18) (Figure 2).

The SALT (Isotonic Solution Administration Logistical Testing) trial compared balanced crystalloids (primarily lactated Ringer's) with 0.9% sodium chloride among 974 adults admitted to a single medical ICU (57). Patients were predominantly admitted from the emergency department (ED) (with sepsis as the most common diagnosis), received primarily saline before ICU admission, and received a median of 1.5 L (IQR, 0.5–3.5 L) of isotonic crystalloid after enrollment. The odds ratio of 30-day in-hospital mortality with balanced crystalloids compared with saline was 0.91 (95% CI, 0.64–1.30). The incidence of death, new renal replacement therapy, or persistent renal dysfunction was lower with balanced crystalloids than with saline among patients who received larger volumes of isotonic crystalloid and among patients with sepsis.

These pilot studies laid the foundation for two recently completed large trials comparing balanced crystalloids with saline among nearly 30,000 acutely ill adults (58, 59). SMART (isotonic Solutions and Major Adverse Renal Events Trial) and SALT-ED (Saline Against Lactated Ringer's or Plasma-Lyte in the Emergency Department) were cluster-randomized, cluster-crossover trials comparing balanced crystalloid (lactated Ringer's or Plasma-Lyte A) with 0.9% sodium chloride for patients in the ICUs and ED at a single academic medical center.

The SMART trial enrolled 15,802 adult patients from five ICUs, 50% of whom were admitted from the ED and approximately 20% of whom were admitted from the operating room (58). Approximately one-fourth of patients were receiving vasopressors, one-third were receiving mechanical ventilation, and 15% had an admitting diagnosis of sepsis or septic shock. Fluid therapy in the ED, operating room, and ICUs was coordinated, so that most patients received the assigned crystalloid during initial resuscitation before ICU admission. Patients received a median of 2.5 L (IQR, 0.8–5.2 L) of intravenous crystalloid between 24 hours before ICU admission and the first of 30 days after ICU admission or hospital discharge. The primary outcome was major adverse kidney events within 30 days (MAKE30): the composite of death, new receipt of renal replacement therapy, or persistent renal dysfunction (60, 61). The National Institute of Diabetes and Digestive and Kidney Diseases work group on clinical trials in acute kidney injury recommends the use of the major adverse kidney events composite outcome to capture effects of acute kidney injury that are more patient centered than acute changes in creatinine, in a manner that appropriately accounts for competing risks (60, 62). Of patients in the balanced crystalloid group, 14.3% experienced MAKE30, compared with 15.4% in the saline group ($P = 0.04$). The 1.1% absolute risk difference in MAKE30 between groups (odds ratio, 0.90; 95% CI, 0.82–0.99) was driven primarily by death (odds ratio, 0.90; 95% CI, 0.80–1.01) and renal replacement therapy (odds ratio, 0.84; 95% CI, 0.68–1.02), not by changes in creatinine (odds ratio, 0.96; 95% CI, 0.84–1.11). In the prespecified subgroup of patients with sepsis or septic shock, 30-day in-hospital mortality was 25.2% with balanced crystalloids and 29.4% with saline (odds ratio, 0.80; 95% CI, 0.67–0.97; $P = 0.02$). Although the relative risk reduction in MAKE30 and in-hospital mortality with balanced crystalloids compared with saline was consistent across the spectrum of baseline risk, for patients at the highest risk of MAKE30 or death, use of balanced crystalloids rather than saline resulted in an absolute risk reduction in MAKE30 of 3.7% (0.6–6.9%) and in-hospital mortality of 4.2% (−7.9% to 16.4%) (63).

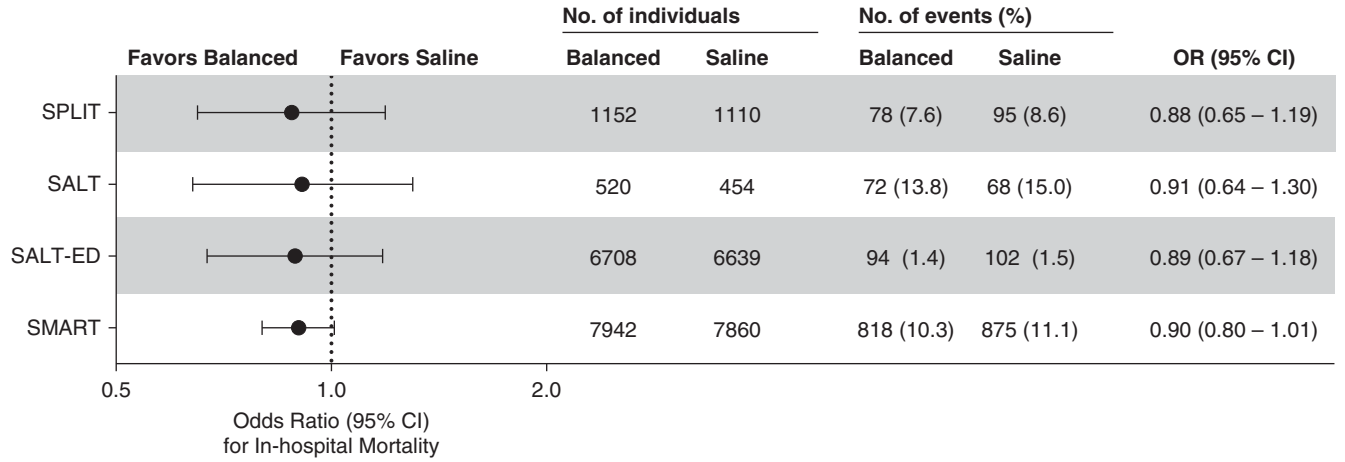

Figure 2. Effect of balanced crystalloids versus saline on mortality among critically ill adults. The odds ratios (ORs) and 95% confidence intervals (CIs) for in-hospital mortality with balanced crystalloids compared with saline are displayed for the four large randomized trials among critically ill adults (56–59).

The SALT-ED trial enrolled 13,347 patients who received intravenous crystalloids in the ED and were hospitalized outside an ICU (59). Patients received a median of 1.0 L (IQR, 1.0–2.0 L) of crystalloid in the ED. Despite the study only controlling choice of crystalloid in the ED, plasma chloride concentrations were lower and serum bicarbonate concentrations were higher in the balanced crystalloid group for at least 72 hours after enrollment. Although the primary outcome of hospital-free days was similar between groups (25 d vs. 25 d; odds ratio, 0.98; 95% CI, 0.92–1.04; $P = 0.41$), the secondary outcome of MAKE30 occurred in 4.7% of patients in the balanced crystalloid group compared with 5.7% of patients in the saline group (odds ratio, 0.82; 95% CI, 0.70–0.95; $P = 0.01$). The difference in acute kidney injury and MAKE30 between balanced crystalloids and saline appeared to be greatest among the prespecified subgroups of patients with hyperchloremia or an elevated plasma creatinine value at ED presentation.

The SMART and SALT-ED trials have important limitations. They were conducted at a single center; fluid was open label; the average volume of crystalloid received was relatively small; and initiation of renal replacement therapy was determined by treating clinicians. Importantly, the trials were not powered to detect differences in each individual component of the MAKE30 outcome, and the MAKE30 composite itself is imperfect because it equally weights three endpoints that are likely valued differently by patients and relies on short-term measures of kidney injury and recovery as surrogates for longer-term kidney function and health status. In both trials, the absolute difference in the MAKE30 outcome between groups was only 1%, suggesting that in an unselected population of adults receiving intravenous fluid, the effects of crystalloid composition on death and severe renal dysfunction are relatively small. Moreover, the trials were not designed to evaluate the mechanism by which crystalloid composition may have influenced the composite MAKE30 outcome. In the SMART trial, differences between the balanced crystalloid group and the saline group in the incidence of hyperchloremia (24.5% vs. 35.6%; $P < 0.001$) and metabolic acidosis (35.2% vs. 42.1%; $P < 0.001$) were modest, suggesting that crystalloid assignment was responsible for around one-third of the observed hyperchloremia and one-sixth of the observed metabolic acidosis. Whether differences between groups in clinical outcomes were mediated by the proposed mechanism of chloride-induced acute kidney injury or by an alternative mechanism is unclear. Potential alternative mechanisms include effects of fluid composition on recovery from established acute kidney injury or the effects of acidosis and chloride-induced inflammation on vasodilation, receipt of vasopressors, and receipt of renal replacement therapy.

Two ongoing trials may provide additional insights into the effect of isotonic crystalloid composition on outcomes among critically ill adults. The PLUS (Plasma-Lyte 148 v Saline) study is a multicenter, parallel-group, blinded, randomized trial comparing Plasma-Lyte 148 with 0.9% sodium chloride with regard to 90-day mortality among 8,800 ICU patients with central access receiving an intravenous fluid bolus for evidence of hypovolemia (64). The BaSICS study (Balanced Solution versus Saline in Intensive Care Study) is a multicenter, parallel-group, blinded, randomized trial comparing Plasma-Lyte 148 with 0.9% sodium chloride with regard to 90-day mortality among 11,000 ICU patients at risk for acute kidney injury with evidence of hypoperfusion and fluid responsiveness (65). Upon completion of these trials, data from randomized trials enrolling more than 50,000 patients will be available to inform the choice between balanced crystalloids and saline for critically ill adults.

Areas of Uncertainty

Specific patient populations exist for whom saline might be expected to produce better outcomes than balanced crystalloids. Despite several preliminary studies of balanced crystalloids for patients with traumatic brain injury (66–69), the hypotonicity of some balanced crystalloids relative to the extracellular fluid makes their safety for patients with elevated intracranial pressure unknown. Administration of isotonic or hypertonic saline to maintain or increase serum osmolarity is an appropriate therapy for patients with elevated intracranial pressure. Saline is an intuitive choice for patients with hypovolemic hyponatremia or hypochloremic metabolic alkalosis, although preliminary data suggest that plasma chloride concentrations may not accurately predict which patients will experience better clinical outcomes with balanced crystalloid versus saline (70). Because most trials comparing balanced crystalloids with saline have occurred in a limited number of academic centers, how the findings generalize to centers with different patient and provider populations in different geographical regions remains uncertain. Although balanced crystalloids and saline are similar in availability and cost in many resource-intensive settings (71), the clinical effects and cost-effectiveness of balanced crystalloids versus saline for patients in low- and middle-income countries may require additional considerations (41).

Balanced crystalloids may be either lactate buffered (e.g., lactated Ringer's) or acetate/gluconate buffered (e.g., Plasma-Lyte, Ringer's acetate). Sodium lactate may cause small increases in serum lactate concentration (72), especially among patients with impaired hepatic function, but it does not cause lactic acidosis and may provide bioenergetic fuel because it is metabolized into carbon dioxide and water, which equilibrate with bicarbonate (73). Similarly, acetate is metabolized through the citric acid cycle into carbon dioxide and water. When used as a dialysate buffer, large doses of sodium acetate may be funneled into alternative metabolic pathways, producing nitric oxide and hemodynamic instability (74), but such effects have not been described at the low rate of acetate administration occurring during intravenous fluid infusion. In contrast, little is known about gluconate metabolism, and some studies suggest that gluconate is predominantly excreted unchanged in the urine, which may limit its alkalinizing effects (75, 76). Whether clinical outcomes or adverse effects differ between balanced crystalloids containing different buffers (77, 78) is the subject of ongoing research (www.clinicaltrials.gov [NCT03537898]).

Whether fluids with greater alkalinizing effects than balanced crystalloids (e.g., isotonic or hypertonic sodium bicarbonate solutions) can improve outcomes for select populations of critically ill adults remains uncertain. Specifically, administration of sodium bicarbonate to critically ill adults with severe acidosis or severe acute kidney injury has a physiologic

rationale, but whether such an approach can prevent renal replacement therapy and death merits further rigorous evaluation (79). Whether other aspects of fluid composition and administration, including osmolarity, temperature, and infusion speed, modify the effect of crystalloid composition on clinical outcomes requires additional research (65).

Conclusions

A growing body of evidence suggests that using balanced crystalloids rather than saline may have the potential to reduce morbidity and mortality for critically ill patients. Preclinical research has demonstrated that administration of saline causes hyperchloremic metabolic acidosis, inflammation, hypotension, acute kidney injury, and death. For patients undergoing major surgery, randomized trials have found that balanced crystalloids cause less hyperchloremic metabolic acidosis and reduce the need for vasopressors. Among acutely ill adults in the ED or ICU, data from several recent large randomized trials suggest that using balanced crystalloids decreases the risk of death or severe kidney dysfunction.

Important questions remain regarding the mechanism by which balanced crystalloids may influence clinical outcomes, which patients are most likely to benefit from balanced crystalloids versus saline, and whether clinical outcomes differ between the available balanced crystalloids. While awaiting the results of further research, the data already available provide clinicians the opportunity to improve care for tens of millions of acutely ill adults treated with intravenous crystalloid solutions each year. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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