Review Article

Balanced crystalloids in the acutely ill patient

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ABSTRACT

Administration of intravenous fluids is the most common therapy given to patients admitted to a hospital. Evidence suggests that the use of normal saline (NS) in large quantities is not without adverse effects. Balanced salt solutions (BSS) contain bicarbonate or one of its precursors that act as a buffer, and the electrolyte composition resembles that of plasma. We reviewed studies across different setups such as intensive care units (ICUs), major surgeries, renal transplants and emergency departments to identify the effect(s) of NS and to find evidence favouring the use of BSS over NS. The use of NS is strongly associated with hyperchloraemic acidosis in almost all the studies. In the largest and latest trial in ICUs, it was found that higher chloride levels were associated with renal injury. No significant difference was found in mortality in any of the trials. In surgical patients, studies found only transient hyperchloraemia and increase in the base deficit in patients receiving NS. Systematic reviews and meta-analyses did not find any significant differences in adverse outcomes such as the need for renal replacement therapy or mortality with the use of saline; however, blood chloride levels were consistently higher with saline compared to BSS. There is a need for larger trials with better methodology to determine if the physiological benefits of BSS translate into better clinical outcomes.

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INTRODUCTION

Almost every patient admitted to a hospital is administered intravenous (i.v.) fluids in some form for one reason or another. Fluids may be given as maintenance therapy, for replacing losses, for patients unable to take adequate fluids orally, for patients with sepsis, during or after surgery, for maintenance of organ perfusion or as a vehicle for drugs.[1] Different fluids have been formulated and tried for these purposes. Starting from normal saline (NS) to Ringer lactate (RL) and balanced salt solutions (BSS); and among colloids, from albumin to different colloids, i.v. fluids have evolved a lot.

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EVOLUTION OF INTRAVENOUS FLUIDS

Historically, this therapy dates back to the cholera outbreak in London in 1831–32. Dr Latta first tried injecting warm water and salts into the large intestine along with intermittent oral feeds. However, he found that there was increased vomiting and purging. He, thus, thought of directly pushing fluid into the circulation. The injected fluid was made of 2–3 drachms of muriate of soda and two scruples of subcarbonate of soda in six pints of water. He injected ounce after ounce of the fluid in an old woman who showed excellent recovery from symptoms.[2–4]

Since then, for over 100 years, i.v. fluids have been an important pillar of treatment in different clinical scenarios. The first fluid to be used was 'normal' saline which is now considered not-so-normal as it is not physiological and is associated with side-effects such as hyperchloraemic metabolic acidosis.

Within half a century of the introduction of i.v. fluids, the next step was lactated fluids (RL/Hartmann solution) which had a bicarbonate precursor. Albumin was used intravenously in 1834. Several colloids were introduced but were rejected due to higher mortality associated with them. Widespread use of i.v. fluids, however, started only after 1950, when Dr David Massa introduced the Rochester needle.[5]

Over the years, it was found that though NS is the most commonly used fluid, its use led to the development of hyperchloraemic acidosis and increased incidence of acute kidney injury (AKI). Thus, there was a shift towards more physiological solution or BSS that would interfere less with the internal milieu and would be easier on the kidneys with lesser biochemical and physical changes.[6,7] The newer BSS have bicarbonate or one of the precursors of bicarbonate (malate, lactate, acetate and gluconate) that acts as a buffer and also potassium, calcium and magnesium that nears the composition of plasma (Table I). As of now, there is no ideal fluid to resuscitate a patient. Each has its advantages and a set of drawbacks. The choice of fluid depends on the clinical condition of the patient and, to a large extent, the physician's choice, in keeping with the locally prevalent practices.

EVIDENCE RELATED TO THE USE OF DIFFERENT INTRAVENOUS FLUIDS

Several studies have been done, and there are many ongoing trials to study the effect of fluids on the acid–base status and renal function, and indirectly on morbidity and mortality of the patients. We review the available studies on this topic.

One of the first studies on humans by Chowdhury *et al*.[8] compared the effects of 2 L of NS with Plasma-Lyte 148, infused over 1 hour each in 12 healthy volunteers in a randomized, controlled, double-blind crossover study. They found sustained hyperchloraemia with NS infusions ($p<0.0001$) along with a fall

TABLE I. Composition of various commercially available intravenous fluids

Intravenous fluid	Osmolarity (mOsm/kg)	pH	Na (mEq/L)	K (mEq/L)	Ca (mEq/L)	Mg (mEq/L)	Cl (mEq/L)	Others (g/L)
0.9% normal saline	308	5.4	154	–	–	–	154	–
Ringer lactate/Hartmann solution*	273	6.5	130–131	4–5	2–4	–	109–111	–
Plasma-Lyte 148†	271	6.5–8	140	5	–	3	98	–
Plasma-Lyte A†	294	7.4	140	5	–	3	98	–
Pentastarch	309	5	154	–	–	–	154	Starch 60
Gelofusine	274	7.4	154	<4	<4	–	125	Gelatin 40
Hemaccel	275–295	7.4	145	5	6.25	–	145	Gelatin 35
5% dextrose‡	252	4 (3.2–6.5)	–	–	–	–	–	–
5% albumin§	310–330	6.9 (0.5)	130–160	<2.5	–	–	130–160	–

* has 28 mEq/L of lactate (avilable as bicarbonate) † has 27 mmol/L of acetate and 23 mmol/L of gluconate ‡ has 50g/L of glucose § bicarbonate and acetate may be present

in strong ion deficit (SID; a measure of metabolic acidosis; p=0.025). Magnetic resonance imaging showed reduction in mean renal artery flow velocity along with reduced renal cortical tissue perfusion in volunteers who received NS infusion. No difference was noted, however, in urinary neutrophil gelatinase-associated lipocalin levels. Expansion of the intravascular space was comparable with both fluids while the expansion of the extracellular fluid compartment was more with 0.9% saline. This implied that saline may be more likely to result in interstitial oedema.[8]

The above study confirmed in humans what had been studied in animals thus far. Elevated extracellular chloride seems to have detrimental effects on vascular resistance, glomerular filtration rate (GFR) and renin activity. The postulated hypothesis is that hyperchloraemia inhibits proximal tubular chloride reabsorption, thus increasing the chloride delivery to the distal nephron. This, in turn, through negative feedback to the afferent renal vessels, decreases renal blood flow. Furthermore, stimulation of the macula densa cells due to elevated tubular chloride concentration, leads to increased afferent arteriolar resistance and decrease in GFR.[9]

Experimental studies apart, several studies in different clinical settings have been conducted, observational and otherwise. The important studies in different settings (intensive care unit [ICU], emergency department [ED], etc.) are summarized below.

STUDIES IN THE ICU (Table II)

Yunos *et al*.,[10] in a prospective, open-label, sequential-period pilot study, studied the association of AKI with administration of chloride liberal fluids (0.9% saline, 4% succinylated gelatin solution or 4% albumin solution) and chloride restrictive fluids (Hartmann solution, Plasma-Lyte 148 and chloride-poor 20% albumin) in critically ill patients. The chloride-restrictive strategy was associated with a significantly lower increase in serum creatinine levels during stay in the ICU. The chloride restrictive group had lower incidence of injury and failure class of risk, injury, failure, loss of kidney function and end-stage kidney disease classification defined AKI and reduced use of renal replacement therapy (RRT; p=0.05). No differences were found in ICU mortality (p=0.42), in-hospital mortality (p=0.44), length of stay in ICU (p=0.52) or long-term dialysis requirements (p=0.95).[10] They extended their original study by 12 months (additional 6 months before and after the change of fluid policy) and found similar results.[11]

Three retrospective studies subsequently found similar results regarding the association of mortality with serum chloride levels. Raghunathan *et al*.[12] (53 448 patients), Shaw *et al*.[13] (109 836 patients) and Zampieri *et al*.[14] (10 249 patients) in their respective studies found a significantly higher rate of mortality in patients with higher levels or with greater rise in serum chloride levels (who either received chloride-rich fluids or NS compared to BSS or RL solution).[12–14]

One of the few studies that did not find any change in the metabolic milieu or outcome was done by Young *et al*. as a double-blind, cluster randomized, double crossover trial in mixed ICUs (medical, surgical, cardiothoracic and vascular surgical)—the SPLIT randomized clinical trial, to determine the effect of buffered crystalloid compared with saline on renal complications. Crossovers occurred so that each ICU used each fluid twice over the 28 weeks of the study; 1152 of 1162 patients (99.1%) receiving buffered crystalloid and 1110 of 1116 patients (99.5%) receiving saline were analysed. They did not find any significant difference in the incidence of AKI (doubling of creatinine or increase by 0.5 mg/dl with levels ≥3.96 mg/dl), use of RRT or hospital mortality (p=0.77, 0.91, 0.40, respectively).[15] Unfortunately, this trial had several limitations. The sample size was not calculated and hence, the study was inadequately powered to detect relatively small, though potentially important, differences in the risk of toxicity between fluid types. The study cohort did not have a large number of patients at increased risk for adverse kidney outcomes. The timing and frequency of serum creatinine measurements were not standardized.

Similarly, two other studies did not find adverse outcomes associated with saline administration. Verma *et al*. conducted a multicentre, double-blind, randomized controlled trial (pilot study) in adult patients who were prescribed crystalloids for resuscitation in ICUs. They studied the difference between NS and Plasma-Lyte 148 administration for up to 4 days after admission to ICU. They found no significant difference between the groups in median base excess (p=0.42), incidence of AKI (p=0.48), peak creatinine levels (p=0.92) and hospital mortality. However, there was significant hyperchloraemia (p=0.01) in the NS group.[16] Semler *et al*. did a cluster randomized, multiple crossover trial of 974 adults to compare saline and balanced crystalloids. Saline (0.9% sodium chloride) and balanced crystalloids (lactated Ringer solution or Plasma-Lyte A) were used alternately on a monthly basis. The parameters studied were major adverse kidney events within 30 days (MAKE30), a composite of death, dialysis or persistent renal dysfunction in relation to the amount of fluid received by the patient. There were no statistically significant differences observed in MAKE30 between the groups (24.7% *v*. 24.6%; p=0.98).[17]

The largest and latest trial was conducted by Semler *et al*.,[18] a pragmatic, cluster randomized, multiple crossover trial in five ICUs, where 15 802 adults were randomized to receive either saline (0.9% NaCl) or balanced crystalloids (RL or Plasma-Lyte

TABLE II. Studies done among patients admitted to intensive care units (ICUs)

Authors	Study type	Fluids studied	*n*	Renal adverse effects	ICU mortality	Hospital mortality	Length of stay	Limitations
Yunos *et al*.[10]	Open label, pilot study	Chloride liberal fluids (0.9% saline, 4% succinylated gelatin solution, or 4% albumin solution) and chloride restrictive fluids (Hartmann solution, PL 148 and chloride-poor 20% albumin)	760 – control; 773 – intervention	Lower increase in serum creatinine levels with chloride restrictive fluids (p=0.05) Long-term HD requirement– not significant	No significant difference	No significant difference	No significant difference	No randomization, half the patients were surgical; non-blinded; open to bias (selection, performance, recall, observer)
Raghunathan *et al*.[12]	Retrospective cohort	Balanced *v.* non-balanced fluids	53 448	No significant difference	Lower with balanced solution	No significant difference	No significant difference	
Shaw *et al*.[13]	Retrospective	NS, RL and other balanced salt solutions	109 836	—	Larger positive shifts in chloride associated with higher mortality (p<0.001)	Mortality tended to increase with greater chloride load	—	Observational study; associations are hypothesis generating; findings may not be generalizable to all SIRS patients because of predefined inclusion criteria
Zampieri *et al*.[14]	Retrospective cohort	RL, NS, D5W, 0.45% NS, 3% NS	10 249: mortality; 8085: AKI	Patients with AKI received proportionately less RL and more D5W; the proportion of NS was similar between AKI` and non-AKI patients	—	Survivors received proportionally more RL and less 0.9% NaCl and D5W than non-survivors		Single-centre database; may limit its external validity; only measured the effects of RL early in the course of critical illness; only studied AKI occurring from days 3 to 7 to guarantee that exposure of interest occurred before outcome; could not study effects of RL on patients with early AKI; could not account for every possible fluid infused, including albumin, blood components, and sodium bicarbonate; As with any observational study, residual confounding because of indication bias may also be present
Young *et al*., SPLIT randomized clinical trial[15]	Double-blind, cluster randomized, double-crossover trial	NS, buffered crystalloid (PL 148)	2278	No significant difference; No significant difference in the probability of requiring RRT	No significant difference	No significant difference	No significant difference	Two-thirds of clinicians were able to correctly guess the assigned treatment; sample size calculations were not done in 4 centres in New Zealand potentially reducing the external validity; >90% of patients exposed to intravenous fluids before enrolment and

(*contd.*)

TABLE II. Studies done among patients admitted to intensive care units (ICUs)

Authors	Study type	Fluids studied	*n*	Renal adverse effects	ICU mortality	Hospital mortality	Length of stay	Limitations
								the majority of pre-enrolment fluid was buffered crystalloid; study cohort did not have significant number of patients at increased risk for adverse kidney outcomes; timing and frequency of serum creatinine measurements not standardized
Verma *et al.*[16]	Multicentre, double blind, RCT (pilot study)	NS, PL 148	70	No significant difference in AKI and peak creatinine levels		No significant difference		
Semler *et al.*, SALT randomized trial[17]	Cluster-randomized, multiple-crossover trial	NS, BSS: RL, PL A	974 (454: NS; 520: BSS)	No significant difference in AKI and peak creatinine levels and need for RRT	MAKE30: composite of death, dialysis and persistent renal dysfunction; no significant difference			Designed as pilot study; not powered to detect small, but potentially meaningful, differences in outcomes; single medical ICU, limits generalizability; study population was extremely broad; RL or PL A together as a single balanced crystalloid group; did not collect data or attempt to control fluid given in the emergency department or operating room before ICU admission; potential concern was whether difference in exposure to saline and balanced crystalloids between groups was large enough to influence outcomes.
Semler *et al.*[18]	Cluster-randomized, multiple-crossover trial	BSS,NS	15 802 (7942: BSS; 7860: NS)	MAKE30 (composite of death dialysis and persistent renal dysfunction) lower in BSS group		No significant difference (818 *v.* 875) p=0.06		Single centre limits generalizability; treating clinicians were aware of composition of the assigned crystalloid and of the group assignment sequence of their ICU; clinician's decision to initiate RRT may be susceptible to treatment bias; RL and PL A taken together and not studied separately

(*contd.*)

TABLE II. Studies done among patients admitted to intensive care units (ICUs) (*contd.*)

Authors	Study type	Fluids studied	*n*	Renal adverse effects	ICU mortality	Hospital mortality	Length of stay	Limitations
Zayed *et al*.[19]	Systematic review and meta-analysis	BSS, isotonic saline	19 332 (6 RCTs)	No significant difference	No significant difference	No significant difference		Some studies were of limited quality given the small sample size in comparison to other studies; patients in each study arm could have received the other fluid type either before enrolment in the operation room or in the emergency department or during the study and this could alter analysis findings; included studies had different designs and only three studies were double-blind randomized controlled trials; follow-up period was variable between studies; results of meta-analysis were affected by one large randomized trial

NS normal saline RL Ringer lactate D5W 5% dextrose PL Plasma-Lyte BSS balanced salt solutions RCT randomized controlled trial
AKI acute kidney injury RRT renal replacement therapy HD haemodialysis MAKE30 major adverse kidney events in 30 days

A)—the SMART trial. MAKE30, a composite of death from any cause, new RRT, or persistent renal dysfunction (defined as an elevation of the creatinine level to ≥200% of baseline) were studied at hospital discharge or 30 days, whichever occurred first. It was found that 1139 (14.3%) of 7942 patients receiving balanced crystalloid had a MAKE30, whereas 1211 of 7860 patients (15.4%) in the saline group had the same and this difference was statistically significant (p=0.04). The incidence of hospital mortality at 30 days (p=0.06), new RRT (p=0.08) and persistent renal dysfunction (p=0.60) were lower in the balanced crystalloid group, though not significant.[18]

In a meta-analysis of randomized controlled trials comparing balanced crystalloids and isotonic saline by Zayed *et al*., primary outcome measures of either hospital mortality or incidence of AKI or both, at the longest follow-up period, were considered.[19] Only prospective randomized controlled trials in an ICU were considered (>19 000 patients from six trials). They did not find any significant difference in the incidence of hospital mortality (11.5% *v*. 12.2%, OR 0.92; 95% CI 0.85–1.01; p=0.09; I^2=0%) or AKI (12% *v*. 12.7%, OR 0.92; 95% CI 0.84–1.01; p=0.1; I^2=0%). Moreover, they did not find any significant difference in overall ICU mortality or the need of new RRT in critically ill patients. One of the limitations of this meta-analysis was that it included a single large trial.

STUDIES IN RENAL TRANSPLANT RECIPIENTS (Table III)

Patients undergoing renal transplantation are administered large volumes of crystalloid in the perioperative period, and the choice of fluid could potentially influence acid–base balance, electrolyte concentration (specifically the incidence of hyperkalaemia) and graft function.

Three randomized trials regarding the choice of fluids administered either during live or cadaveric renal transplant found that balanced solutions only provided a better acid–base balance or biochemical profile in patients with no significant differences in the incidence of reduced urine output, renal failure, need for dialysis, mortality or graft rejection. All the three trials deemed NS to be equally safe for use in patients undergoing renal transplant.[20–22]

Wan *et al*., in a Cochrane review of six studies comprising 477 participants, reviewed the use of different i.v. fluids in renal transplant patients. Incidence of hyperchloraemic acidosis was higher in patients who received NS in the perioperative period.[23]

Contrary to the above studies, a retrospective study by Adwaney *et al*. of 97 patients who had undergone renal transplant showed that patients receiving Plasma-Lyte were less likely to need emergency RRT (OR 0.15; p=0.004) compared to those receiving NS. Patients receiving Plasma-Lyte had a lower incidence of hyperkalaemia, acidosis, length of stay and better graft function at 3 months and better diuresis than those who received NS.[24]

STUDIES IN PATIENTS UNDERGOING MAJOR ABDOMINAL SURGERIES (Table IV)

Early data on the effects of infusing NS came from the operating room. In an early study conducted by McFarlane and Lee,[25] 30 patients undergoing hepatobiliary or pancreatic surgeries were randomized to receive saline or Plasma-Lyte 148. Patients administered saline had significantly higher chloride levels, lower

standard bicarbonate and higher base deficit. The authors opined that exclusive administration of saline could give a temporary hyperchloraemic acidosis which could be interpreted as being pathological. Similar results were seen in 40 patients randomized to receive a 1:1 mixture of balanced crystalloids and balanced colloids and compared with unbalanced crystalloid (buffer-free Ringer solution containing chloride 155.5 mEq/L) for goal-directed therapy during elective hip replacement surgery.[26]

In a retrospective cohort study of a large American database, Shaw *et al*. studied over 30 000 patients who received i.v. fluids for major open abdominal surgeries.[27] They found significantly lower incidence of hospital mortality in patients who received balanced solutions (2.9%) in comparison to patients who received NS (5.6%, p<0.001). Further, receipt of balanced fluids was associated with a lower incidence of complications (OR 0.79, 95% CI 0.66–0.97), specifically lower postoperative infections (p=0.006), lower incidence of renal failure requiring dialysis (p<0.001), blood transfusions (p<0.001), electrolyte disturbances (p=0.046) and acid–base abnormalities (p=0.02).

Song *et al*. randomized 50 patients undergoing spinal fusion surgery to receive either 0.9% saline or Plasma-Lyte in the perioperative period. The outcomes measured included coagulation abnormalities, intraoperative blood loss, acid–base status, electrolytes and renal functions. In contrast to Plasma-Lyte, fluid therapy with 0.9% saline resulted in transient hyperchloraemic acidosis, while coagulation tests and the amount of blood loss were similar in the groups.[28]

There are two Cochrane systematic reviews regarding the use of i.v. fluids in the perioperative period; one by Burdett *et al*. published in 2012 and the other by Bampoe *et al*. in 2017.[29,30] Randomized trials of buffered versus non-buffered fluids given in the perioperative period were included, with 706 patients in the first review and 1096 patients in the second. No significant difference was found with respect to mortality and postoperative need of RRT with either fluid. The only difference between the groups was a significantly higher incidence of hyperchloraemic acidosis in patients who received NS. However, this difference was corrected by postoperative day 1. In addition, Burdett *et al*. did not find any difference in intraoperative blood loss or transfusion requirement and length of hospital stay.

TABLE III. Studies done among renal transplant recipients

Authors	Study type	Fluids studied	*n*	Renal adverse effects	Hyper-chloraemia	Metabolic acidosis	Hyper-kalaemia	Limitations
Hadimioglu *et al*.[20]	Randomized, double-blind study	NS, RL, PL	90	No significant difference	Significant in NS	Significant fall in BE only in NS	No significant difference	–
Kim *et al*.[21]	Randomized controlled trial	NS, PL	60	Postoperative serum creatinine and 24-hour urine output were similar between the groups	Significant in NS	Significant fall in pH and BE in NS in post-reperfusion period		Only included patients undergoing elective living donor kidney transplantation; type of fluid administered was specified only during surgery
Potura *et al*.[22]	Randomized controlled trial	NS, acetate buffered balanced solution	150	No significant difference in urine output, serum creatinine and need for haemodialysis till day 7	Significant in NS	Significantly lower BE in NS group	No significant difference	Open-labelled design; short follow-up; randomization was not available 24×7
Wan *et al*.[23]	Systematic review	NS, BSS In 2 studies, bicarbonate was added to NS to prepare a buffered solution	477 (6 studies)	No difference in the risk of delayed graft function in 3 studies	Significantly higher in NS in 3 studies	pH higher in BSS group in 3 studies bicarbonate levels higher in BSS group in 3 studies	No difference in 2 studies No difference in post-operative potassium levels in 4 studies	Low number of studies analysed; no study reported on the total volume of fluid delivered to study participants; overall quality of evidence included was low to moderate; duration of follow-up for all included studies was very short
Adwaney *et al*.[24]	Retrospective	NS, PL	97 (59 NS *v.* 38 PL)	Patients in PL group were less likely to require emergency post-operative dialysis than those receiving 0.9% saline; better graft function at 3 months in PL group	Significantly higher in NS	Significantly higher in NS	Significantly higher in NS	Not randomized and small sample size; limited to one centre

NS normal saline RL Ringer lactate D5W 5% dextrose PL Plasma-Lyte BSS balanced salt solutions BE base excess

STUDIES IN TRAUMA AND EMERGENCY (Table V)

Among other patients who require large volumes of resuscitation fluids are those with trauma and/or presenting to the ED. Young *et al*. randomized 65 adult trauma patients requiring blood transfusion, tracheal intubation or surgery within 60 minutes of arrival to their centre to receive either saline or Plasma-Lyte A for resuscitation in the first 24 hours after injury. They hypothesized that Plasma-Lyte A would better correct the base deficit 24 hours after injury. The mean improvement in base excess from 0 to 24 hours was significantly greater with Plasma-Lyte A than with NS, arterial pH was greater and serum chloride was lower with Plasma-Lyte A than with saline. However, there was no significant difference with respect to mortality, volumes of study fluid administered and 24-hour urine output.[31]

In a randomized double-blind pilot study, Roquilly *et al*. compared saline to balanced solution in 42 severely brain-injured patients (who received the fluid for 48 hours).[32] There was a higher incidence of hyperchloraemic acidosis and lower SID within 48 hours in the patients who received NS in comparison to those who received balanced solution. Importantly, intracranial pressure was not different between the two groups, though this study was not powered for this endpoint.

Self *et al.* compared BSS (RL and Plasma-Lyte A) with NS in a single-centre, pragmatic, multiple crossover trial of saline against RL or Plasma-Lyte in the ED.[33] Clinical effects of crystalloids were studied in the ED among non-critically ill patients. Patients receiving <500 ml of crystalloids were excluded. The primary outcome studied was hospital-free days to day 28, and the secondary outcomes were MAKE30, AKI of stage 2 or higher according to the Kidney disease: Improving global outcomes guidelines and hospital deaths. No difference in the groups was observed in hospital-free days (median 25 days in both groups; adjusted OR with balanced crystalloids 0.98; 95% CI 0.92–1.04; p=0.41). However, balanced crystalloids resulted in lower incidence of MAKE30 than saline (4.7% *v*. 5.6%; adjusted OR 0.82; 95% CI 0.70–0.95; p=0.01). The limitations of this study were that it was done at a single centre and was not blinded. Further, detailed patient information was not available and fluids given to patients after being moved from ED were not controlled.[33]

TABLE IV. Studies among patients undergoing major abdominal surgeries

Authors	Study type	Fluids studied	*n*	Renal adverse effects	Hyper-chloraemia	Metabolic acidosis	Mortality/ length of stay	Limitations
McFarlane and Lee[25]	RCT	NS and PL 148	30	No significant difference in urine levels	Significantly higher in NS group	Significantly low bicarbonate and increased base deficit in NS group		Single centre with small sample size
Krebbel *et al*.[26]	Prospective, double-blind, randomized, controlled study	Unbalanced crystalloid (chloride: 155.5 mmol/L) 1:1 mixture of a balanced crystalloid and a balanced colloid (6% w/v hydroxyethyl starch 130/0.42; chloride: 98 and 112 mmol/L, respectively)	40	No significant difference in serum creatinine at 1 h and 6 h after surgery between the two groups and also on postoperative day 1; NGAL concentration showed no significant difference	Significantly higher in unbalanced group	pH and SBE significantly lower in unbalanced group	No signi-ficant difference in hospital stay	Small sample size and single centre; study done in patients treated within a highly standardized clinical pathway undergoing surgery with rather low blood loss. It is not clear whether these results would also be valid or even more pronounced in major and/or longer lasting operations with a greater volume turnover
Shaw *et al*.[27]	Retrospec-tive cohort study	NS, PL	30 994: NS; 926:BSS	Renal failure requiring dialysis significantly higher in NS group	Significantly higher in NS group	Significantly higher incidence of acidosis in NS group	Significantly higher in NS group	Only 12% of patients received purely saline or purely balanced solution; patients in the 0.9% NS group were more likely to have undergone emergency surgery; propensity scoring to correct bias is not perfect; inter-pretation of results requires appreciation of clinical context

NGAL neutrophil gelatinase associated lipocalin (*contd.*)

TABLE IV. Studies among patients undergoing major abdominal surgeries (*contd.*)

Authors	Study type	Fluids studied	*n*	Renal adverse effects	Hyper-chloraemia	Metabolic acidosis	Mortality/ length of stay	Limitations
Song *et al*.[28]	RCT	NS, PL	50	Intraoperative urine output was greater in patients who received PL; creatinine levels at postoperative 24 hours not significantly different	Significantly higher in NS group	Significantly lower pH, base excess and bi-carbonate levels in NS group	No significant difference in hospital stay	Patients of both groups received 900 ml of HES; study was not double-blinded
Burdett *et al*.[29]	Systematic review	Buffered *v.* non-buffered i.v. fluids	14 trials (706 patients)	No significant difference (3 trials)		Significantly lower pH in non-buffered group	No significant difference in mortality (3 studies; 267 patients); No significant difference in length of stay (5 trials)	Patient number in trials low; 5 trials used colloid in experimental and control arm; only 5 trials studied completely buffered against completely non-buffered; heterogeneous data: 2 studies included renal transplants; not all mentioned the method of blinding; 3 studies had no blinding
Bampoe *et al*.[30]	Systematic review	Buffered *v.* non-buffered i.v. fluids	19 publications of 18 RCTs (1096)	Low-quality evidence regarding renal dysfunction needing RRT	Moderate evidence with non-buffered group	Moderate evidence of lower pH in non-buffered group	Low-quality evidence regarding mortality	Significant clinical and statistical heterogeneity; 5 studies were of renal transplant; Few addressed mortality and organ dysfunction

NS normal saline RL Ringer lactate D5W 5% dextrose PL Plasma-Lyte BSS balanced salt solutions HES hydroxyethyl starch
RCT randomized controlled trial SBE standard base excess i.v. intravenous

RECENT META-ANALYSES

An effective method of summarizing results of individual trials comes from systematic reviews and meta-analysis. A few meta-analyses have summarized the effects of balanced fluids in comparison to saline in perioperative and ICU patients. Spurious conclusions in systematic reviews with traditional meta-analyses can be reduced using trial sequential analysis (TSA). Several empirical studies have demonstrated that the TSA provides better control of type I errors and of type II errors than the traditional naïve meta-analysis.

A systematic review and meta-analysis of randomized trials comparing fluid resuscitation with balanced solutions versus isotonic saline by Serpa Neto *et al*. included eight trials in operation rooms and three in ICUs. The analysis of these trials involving 2703 patients did not find any significant difference in the incidence of hospital mortality, the occurrence of AKI and the need of RRT. However, significantly lower chloride levels were found in patients receiving BSS (although without any change in arterial pH).[34]

Kawano-Dourado *et al*.[35] did a systematic review and included trial sequential analyses to assess the risk of bias of individual trials and the overall quality of evidence. They assessed whether the use of low chloride solutions in unselected critically ill or perioperative adult patients for maintenance or resuscitation reduces mortality and RRT use when compared to high-chloride fluids. A total of 3710 patients were included in the mortality analysis and 3724 in the RRT analysis. No significant difference in mortality (OR 0.90; 95% CI 0.69–1.17; p=0.44; I^2=0%) or RRT use (OR 1.12; 95% CI 0.80–1.58; p=0.52; I^2=0%) was found.[35] However, the authors opined that the overall pooled sample size was small and the volume of study fluid was limited; thus, the data were underpowered to detect potentially important differences.

Similar results were found in a systematic review and meta-analysis with TSA of nine trials (six ICU based, two focused on acute pancreatitis and one included trauma patients) by Liu *et al*.[36] A total of 19 203 patients who received either balanced crystalloids (RL, Plasma-Lyte A and Plasma-Lyte 148) or NS were analysed for mortality, AKI and RRT use. However, the TSA did not provide any conclusive evidence favouring the findings.

The above findings were refuted in a meta-analysis with TSA of eight studies by Xue *et al*.;[37] which included 19 301 patients and compared balanced crystalloids with NS in critically ill adults. The authors showed significantly longer RRT-free days (p<0.001), less risk of increase in serum concentrations of chloride (p<0.001), less risk of decline in serum base deficit (p=0.004), longer ventilator-free days (p<0.001) and vasopressor-free days (p=0.02) in patients who received balanced crystalloids. Survival in hospital did not show any statistically significant difference (p=0.06) between the two groups. However, subgroup analysis favoured improved survival in the BSS group in septic patients (p=0.02) and non-traumatic brain injury patients (p=0.02). In this study too, TSA did not find conclusive evidence and warranted a larger sample size.

TABLE V. Studies done among patients with trauma and/or admitted to the emergency department

Authors	Study type	Fluids studied	*n*	Renal adverse effects	Hyper-chloraemia	Metabolic acidosis	Mortality/ length of stay	Limitations
Young *et al*.[31]	Randomized controlled trial (RCT)	NS, Plasma-Lyte A	46 (65 rando-mized)	Greater urine output in first 6 hours in PL group; no significant difference in 24 h urine output	Significantly elevated in NS group	Acidaemia corrected in 6 hours in PL group but persisted for 24 hours in NS group; correction of base deficit from 0 to 24 hours was significantly greater with Plasma-Lyte A than with 0.9% NaCl	No signi-ficant difference in mortality	Pilot study, not sufficiently powered; treating physicians had unlimited access to patient laboratory data and controlled the rate of fluid administration. This may have affected some outcomes of interest. Failure to randomize some of the eligible subjects
Roquilly *et al*.[32]	Single-centre, two-arm, double-blind, pilot RCT	NS, balanced solutions	42 (2 excluded)		Significantly higher in NS group	Significant fall in pH and SID in NS group	No signi-ficant difference in mortality	Conclusions only valid for traumatic brain injury patients; did not report differences between groups regarding side-effects of hyperchloraemic acidosis; reported biological differences may not be clinically relevant; balanced solution did not alter neurological recovery; not adequately powered; single-centre trial
Self *et al*., SALT-ED trial[33]	Single-centre, pragmatic, multiple-crossover trial	NS *v.* balanced crystalloid (RL or PL)	13 347	No significant difference in serum creatinine levels	Significantly higher in NS group	Significantly low bicarbo-nate levels in NS group	No significant difference in hospital-free days; MAKE30– significantly lower in balanced crystalloid group	Single-centre, unblinded trial; detailed information about patient characteristics not available—data collection from electronic records; fluids administered after hospital admission and those used as medication carriers were not controlled; in balanced crystalloid wing, RL was used for 95% of patients; fluid selection tailored to specific patient characteris-tics is an alternative approach that was not evaluated

NS normal saline RL Ringer lactate SID strong ion deficit/difference MAKE30 major adverse kidney event within 30 days PL Plasma-Lyte

Huang *et al*. did a meta-analysis of nine trials (871 patients) comparing BSS and NS in non-renal surgical patients.[38] BSS provided significantly better acid–base balance and lower chloride values than NS.

STUDIES AMONG CHILDREN (Table VI)

Literature is scarce regarding the choice of crystalloids for acutely ill children. Most recommendations extrapolate studies available

among adults and suggest that balanced fluids may be safer for fluid resuscitation.[39]

In a matched retrospective cohort study from 382 American hospitals for children, data from 12 529 children with severe sepsis/septic shock was studied. Outcomes were compared between children who received RL during resuscitation to those who received NS. There were no differences in 30-day hospital mortality, AKI or need for new dialysis. The patients who received any amount of RL had a longer hospital stay of 2.4 days (95% CI 1.4–5 days; $p<0.01$).[40] This could possibly be attributed to the larger crystalloid volumes received by this group of patients.

A few small randomized trials in different settings (diarrhoeal dehydration, diabetic ketoacidosis) showed mixed results. However, it is important to note that these studies compared RL to NS. Twenty-two children with acute diarrhoeal, severe dehydration were randomized to receive either RL or NS for fluid resuscitation. There was no difference in improvement in pH over the baseline between RL and NS, though the volume of fluid required in the RL group was lesser.[41] In a similar study, among 68 children with acute diarrhoea and severe dehydration, resuscitation with RL or NS was associated with similar clinical improvement and resolution of pH. No significant differences were observed in secondary outcomes in electrolytes, renal and blood gas parameters, median time to start oral feeding and hospital stay.[42]

In a randomized controlled open trial, 240 children between 1 and 36 months undergoing major surgery were assessed for changes in plasma chloride concentrations using either NS or a balanced crystalloid solution (sterofundin) intraoperatively. The mean change in chloride levels was greater in the NS group (median 4; interquartile range [IQR] 2, 6) compared to the sterofundin group (median 2; IQR 1, 49; $p=0.0001$). Changes in serum magnesium were also lesser in the sterofundin group ($p<0.001$). No other significant electrolyte differences or change in urea/creatinine levels were seen.[43]

In another trial in children undergoing resection of brain tumours, 53 children between 6 months to 12 years were randomized to receive either NS or Plasma-Lyte A during and for 24 hours after surgery. Children in the saline group had an increase in serum chloride and base excess postoperatively, but this hyperchloraemic metabolic acidosis resolved by day 1 postoperatively. There was no difference in brain oedema (as assessed by the neurosurgeons). There was no significant renal dysfunction noted.[44]

ON-GOING AND NEW TRIALS

The BaSICS trial by Zampieri *et al*. aims to provide an answer to whether a balanced crystalloid, compared with saline, improves 90-day all-cause mortality in critically ill patients. Further, the effect of a slow infusion rate as against a rapid infusion rate would also be tested. A total of 11 000 patients will be recruited from nearly 100 ICUs in Brazil.[45]

The PLUS trial by Hammond *et al*. will study the effect of Plasma-Lyte and saline on 90-day all-cause mortality and several other secondary outcomes in about 50 ICUs in Australia and New Zealand.[46]

CONCLUSION

Intravenous fluids are not without side-effects and judicious use is required, as with all other drugs. It is still inconclusive if the high chloride load is only because of the type of i.v. fluid. There is enough evidence that NS causes biochemical disturbances and may predispose to renal injury. Small effect sizes for biochemical outcomes and lack of correlated clinical follow-up data mean that robust conclusions on major morbidity and mortality associated with buffered versus non-buffered fluid choices are still lacking. Larger studies are needed to assess these relevant clinical outcomes.

Several aspects of i.v. fluid therapy remain unexplored. Further studies are needed to explore if the rate of fluid administration, the time and volume of fluid administered have any role in these biochemical changes, renal injury or mortality.

Hence, the results of the on-going trials are awaited for any conclusive evidence for better outcomes in administering particular types of i.v. fluids, a necessary component of patient care.

Conflicts of interest. None declared

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TABLE VI. Studies among children

Authors	Study type	Fluids studied	*n*	Renal adverse effects	Hyper-chloraemia	Metabolic acidosis	Mortality/ length of stay	Limitations
Weiss *et al*.[40]	Retrospective cohort study	NS, RL (exclusive or along with NS)	12 529 (382 hospitals); 10 379: NS; 2150 at least 1 RL+NS; 459 RL only	No significant difference in matched analysis			Unadjusted 30 days mortality: no significant difference between NS group and NS+RL group; unadjusted 30 days mortality significantly lower in RL only group; significantly longer hospital stay for RL+NS group in comparison to NS group; significantly lower hospital stay in RL alone group	Data based on insurance claims; may have led to misclassification bias not able to account for pre-hospital fluid administration; ICD-9-CM codes for infection plus organ dysfunction to identify paediatric sepsis controversial; differences in demographics, comorbid conditions and intensive therapies indicate non-random selective use of RL over NS
Mahajan *et al*.[41]	Double-blind RCT	NS, RL	22			No significant difference in improvement of pH		Small sample size; single centre
Kartha *et al*.[42]	Double-blind RCT	NS, RL	68	No significant difference	No significant difference	No significant difference		Two-thirds of patients had received some form of treatment before enrolment; sample size based on study which had sicker patients than this study
Disma *et al*.[43]	Multicentre RCT	NS, sterofundin	240	No significant difference	Significantly high in NS group			
Lima *et al*.[44]	RCT	NS, BSS	53	No significant difference	Significantly higher in NS group	Significantly high base deficit in NS group; significantly high hyperchloraemic acidosis in NS group		Underpowered to study outcomes such as incidence of AKI, mortality; attending physicians were not blinded; study was carried out in a tertiary university-affiliated hospital in concert with procedures of high complexity and long duration

NS normal saline RL Ringer lactate PL Plasma-Lyte BSS balanced salt solutions RCT randomized controlled trial AKI acute kidney injury ICD International classification of diseases

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