

# Fluid Therapy and Outcome: Balance Is Best

Sara J. Allen, FANZCA, FCICM

Department of Anaesthesia and the Cardiothoracic and Vascular Intensive Care Unit, Auckland City Hospital, Auckland, New Zealand

Presented at Winter Meeting Perfusion Downunder 2013, Hayman Island, Queensland, Australia, September 1–3, 2013.

---

**Abstract:** The use of intravenous fluids is routine in patients undergoing surgery or critical illness; however, controversy still exists regarding optimum fluid therapy. Recent literature has examined the effects of different types, doses, and timing of intravenous fluid therapy. Each of these factors may influence patient outcomes. Crystalloids consist of isotonic saline or balanced electrolyte solutions and widely distribute across extracellular fluid compartments, whereas colloids contain high-molecular-weight molecules suspended in crystalloid carrier solution and do not freely distribute across the extracellular fluid compartments. Colloids vary in composition and associated potential adverse effects. Recent evidence has highlighted safety and ethical concerns regarding the use of colloid solutions in critically ill patients,

particularly the use of synthetic starch solutions, which have been associated with increased morbidity and mortality. Crystalloid solutions with a chloride-rich composition (e.g., isotonic saline) have been associated with metabolic acidosis, hyperchloremia, increased incidence of acute kidney injury, and increased requirement for renal replacement therapy. An optimum dose of intravenous fluids remains controversial with no definitive evidence to support restrictive versus liberal approaches. Further high-quality trials are needed to elucidate the optimum fluid therapy for patients, but currently a balanced approach to type, dose, and timing of fluids is recommended. **Keywords:** cardiopulmonary bypass, kidney, outcomes, perioperative care, resuscitation. *JECT. 2014;46:28–32*

---

Administration of intravenous fluids is routine in the management of surgical and critically ill patients. Recent published randomized controlled trials and systemic reviews have examined the efficacy, morbidity, and mortality associated with the use of different types, timing, and doses of intravenous fluids and suggest that each of these factors may influence outcomes for patients (1–6). However, controversies still exist with regard to the ideal type, dose, and timing of intravenous fluid for perioperative and critically ill patients.

This review re-examines the evidence to date with particular focus on current best practice in the specialties of perfusion, anesthesia, and critical care and on how a balanced approach to all domains of fluid administration may positively influence clinical outcomes.

## TYPES OF FLUID: CRYSTALLOID VERSUS COLLOID

### Definitions

Crystalloid fluids consist of isotonic saline (e.g., 0.9% saline, normal saline) or balanced electrolyte solutions

(e.g., Plasmalyte, Ringer's lactate) and are considered to rapidly and widely distribute across the extracellular fluid compartments after administration. Colloids are fluids with a crystalloid carrier solution containing suspended large-molecular-weight molecules, which do not freely diffuse across the extracellular fluid compartments (e.g., albumin, hydroxyethyl starch) and therefore exert colloid oncotic pressure. Colloids have traditionally been thought to remain in the intravascular fluid compartment for a prolonged period after administration in contrast to crystalloids. Thus, colloids have been used as volume-sparing agents with the proposed benefits of less overall volume required for resuscitation and restoration of intravascular volume and therefore less interstitial edema and possibly less hemodilution for patients. However, several factors may alter the distribution of colloid solutions, including patient volume status, the integrity of the vascular endothelium, systemic inflammation, and the use of alpha-adrenergic agonists and therefore alter the effectiveness of colloids as volume-sparing agents.

### Colloid Subtypes: Albumin, Gelatins, and Synthetic Starches

Within colloids are several subtypes of fluid. Albumin is a fluid containing the human plasma protein, derived from pooled human plasma, most commonly in 4% solution and usually suspended in isotonic saline, while synthetic

---

Received for publication November 17, 2013; accepted February 9, 2014. Address correspondence to: Sara J. Allen, FANZCA, FCICM, Greenlane Clinical Centre, Auckland City Hospital, Private Bag 92024, Auckland Mail Centre, Auckland, New Zealand 1142. E-mail: saraa@adhb.govt.nz The author has stated that she has reported no material, financial, or other relationship with any healthcare-related business or other entity whose products or services are discussed in this paper.

colloids such as Hespan<sup>®</sup>, Voluven<sup>®</sup>, and Volulyte<sup>®</sup> contain 6% hydroxyethyl starch (HES) derived from plant sources, suspended in balanced crystalloid solution. Older colloids include Haemaccel<sup>®</sup> and Gelofusin<sup>®</sup> containing succinylated gelatin molecules derived from animal sources and suspended in balanced crystalloid solutions. Each type of colloid has potential risks associated with use; albumin as a blood product has a potential risk of infection and synthetic colloids have potential risks of coagulopathy, end organ damage, and anaphylactoid reactions. The composition of commonly administered fluids is summarized in Table 1.

### Outcomes

Several large randomized controlled trials have recently examined the use of crystalloid versus colloid solutions. Important differences according to which colloid was used have been demonstrated.

In 2004, the SAFE Study, a large multicenter randomized controlled trial, investigated the use of .9% saline versus 4% albumin for fluid resuscitation in 6997 intensive care patients. Total fluid administration between the two groups differed over the first 4 days with a ratio of volume of albumin to volume of saline of 1:1.4. This represented an approximate mean difference of 800–900 mL of fluid over this time, a clinically modest amount. No differences in overall mortality or outcomes at 28 days were demonstrated, although in preplanned subgroup analysis, albumin was associated with differential outcomes (adverse outcome in traumatic brain injury, improved outcome in severe sepsis) (2).

The use of colloids has traditionally been recommended as a method of minimizing total volume of fluid required for resuscitation in comparison with crystalloids. The expected ratio of volume of crystalloid to colloid administered for the same degree of intravascular fluid expansion is approximately 5–1. However, as highlighted, trials have demonstrated that the estimated additional volume expansion with colloids in place of crystalloids is much smaller in vivo than estimated based purely on physicochemical

properties and Starling's Laws (1,2). This reflects the fact that the endothelial glycocalyx layer is damaged in many critically ill and surgical patients and is unable to maintain full integrity. The endothelial glycocalyx is a delicate layer of glycoproteins, glycosaminoglycans, proteoglycans, and associated plasma proteins, present on endothelial cells, and is vital in determining endothelial permeability. This layer is easily damaged by inflammation (e.g., surgery, sepsis, and critical illness), ischemia, hyperglycemia, and by exposure to altered intravascular volume status (e.g., during cardiopulmonary bypass). Damage to the endothelial glycocalyx causes increased endothelial permeability and allows more rapid diffusion of molecules and carrier fluid into the interstitium than would otherwise be predicted. Also, injury to the glycocalyx may be associated with increased inflammation and loss of vascular responsiveness (7). The crystalloid to colloid ratio is estimated from large trials to be only 1.2–1.4–1 (1,2). Additional to interstitial edema resulting from administration of all fluids, there is significant concern regarding tissue injury with synthetic colloids as a result of accumulation of synthetic molecules in the interstitium after breaching the endothelium with toxic effects previously described in the kidney, liver, and bone marrow (8).

In 2012, the 6S Trial Group and the Scandinavian Critical Care Trials Group reported results from a large multicenter, parallel-group, randomized, blinded trial comparing fluid resuscitation in the intensive care unit with 6% HES versus Ringer's acetate in 798 patients with severe sepsis (8). This study demonstrated increased risk of mortality at Day 90 (relative risk 1.17) and increased risk of renal replacement therapy (relative risk 1.35) in patients treated with HES. Additionally, patients treated with HES received more allogeneic blood product transfusions. There were no differences in the total volumes of fluid used between the two groups. A further study published in 2012 compared the use of HES or .9% saline for resuscitation in intensive care (1). A total of 7000 patients admitted to an intensive care unit (ICU) were randomly allocated to receive 6% HES or .9% saline for all fluid resuscitation

**Table 1.** Composition of common crystalloid and colloid fluids [5].

Electrolyte (mmol/L)	Plasmalyte	Normal Saline	Ringer's Lactate	Albumin 4%	Voluven Hydroxyethyl Starch 6%	Gelofusin
Sodium	140	154	131	140	154	154
Potassium	5	0	5	0	0	0
Chloride	98	154	111	128	154	125
Calcium	0	0	2	0	0	0
Magnesium	1.5	0	1	0	0	0
Bicarbonate	0	0	0	0	0	0
Lactate	0	0	29	0	0	0
Acetate	27	0	0	0	0	0
Glucuronate	23	0	0	0	0	0
Octanoate	0	0	0	6.4	0	0

until discharge from the ICU. There was no significant difference in mortality between the two groups but an increased use of renal replacement therapy in patients treated with HES. Additionally, an increase in adverse events (e.g., pruritus, skin rash) occurred in the HES-treated group. There was again only a modest difference in the volume of fluid administered between groups.

In a recent randomized study of patients undergoing elective cardiac surgery, infusion of 5% albumin solution was compared with 6% HES and Ringer's lactate in doses of up to 50 mL/kg/day with outcomes of blood loss through chest drainage tubes, hemodilution, coagulation abnormalities, and total blood transfusions compared (9). HES and 5% albumin use were associated with increased hemodilution, adverse effects on coagulation, and increased transfusion of blood products compared with Ringer's lactate use.

It is important to recognize that the use of both crystalloid and colloid solutions for resuscitation is as an alternative to blood and blood product transfusion. Whereas a discussion of transfusion therapy is beyond the scope of this review, it is worth noting that multiple factors, including increased cost, limited resource availability, and associations with increased morbidity and mortality with blood and blood product use, contribute to the use of crystalloids and colloids. Conversely, however, use of both colloids and crystalloids in excess are associated with hemodilution and its adverse effects: dilutional coagulopathy and dilutional anemia. In a study of 108 patients undergoing coronary artery bypass grafting, profound hemodilution (hematocrit 5–18% on cardiopulmonary bypass) compared with moderate hemodilution (hematocrit  $\geq 27\%$  on cardiopulmonary bypass) was associated with increased neurocognitive decline, but the moderate hemodilution group was associated with greater incidence of blood transfusion and pulmonary complications (10). These findings illustrate well the dilemma of transfusion therapy; that is, too much blood may be deleterious, but too little blood may well have even worse effects. The optimum or even minimum safe levels of hematocrit are not yet established.

### Conclusions

Overall, the use of synthetic colloids in critically ill patients confers no benefit and is associated with significant harm and increased cost. Several organizations including the Federal Drug Agency of the United States and the European Medicines Agency have issued statements and guidelines recommending the cessation of synthetic colloid use in critically ill patients, patients with sepsis, and those with renal dysfunction (11–13). The Medicine and Healthcare products Regulatory Agency of the United Kingdom (MHRA) suspended the use of HES for all patients in June 2013. The manufacturers of Hespan<sup>®</sup> include a warning in the package insert that it is not recommended for use in cardiopulmonary bypass or

patients undergoing cardiac surgery as a result of the potential bleeding risks. Whereas the use of these fluids in noncritically ill and routine surgical patients is not as well studied, given the absence of documented benefit, potential for harm, and clearly increased cost compared with crystalloid solutions, their use is not recommended. In this author's institution, synthetic colloids have been removed from the hospital formulary. In addition, because albumin has been demonstrated as a safe colloid fluid in most critically ill patients, it may be used in the limited number of patients in whom a benefit is expected in modest volume-sparing and prolongation of intravascular expansion.

### CRYSTALLOID SOLUTIONS: BALANCED ELECTROLYTE SOLUTIONS VERSUS ISOTONIC SALINE

Recently, research regarding optimal fluid therapy has focused on the use of balanced crystalloid solutions (e.g., Ringer's acetate, Plasmalyte) in comparison with normal saline as a result of concerns regarding the deleterious effects of administration of normal saline, particularly in relation to metabolic, gastrointestinal, renal, and coagulation side effects.

#### Isotonic .9% (normal) Saline

Normal saline contains 154 mmol/L sodium and 154 mmol/L chloride ions with an osmolality of 287 mOsm/kg H<sub>2</sub>O (identical to plasma osmolality). Infusion of large volumes of isotonic saline (e.g., cardiopulmonary bypass prime, fluid replacement intraoperatively) therefore results in a chloride load and dilution of plasma anions causing dilutional hyperchloremic metabolic acidosis.

#### Balanced Solutions

Different balanced solutions exist; however, all have electrolyte compositions similar to that of plasma, as outlined in Table 1. Organic anions such as lactate, acetate, and gluconate are used as buffers to provide in vitro isotonicity but are rapidly metabolized after intravenous infusion, resulting in decreased osmolality in vivo. Infusion of large volumes of balanced crystalloid solutions does not produce a large chloride load and has less dilution effect (because rapid diuresis is evoked by suppression of anti-diuretic hormone release, which occurs as a result of the in vivo hypotonicity). Balanced solutions therefore have preserved acid-base homeostasis, and chloride levels remain normal.

#### Outcomes

Controversy exists regarding the metabolic acidosis induced by saline, whether the acidosis affects clinical outcomes or is simply a side effect of saline, which is transient and benign. There is currently no clear evidence to elucidate

this. However, the effects of excess chloride resulting from saline administration are more clearly understood.

### **Renal and Gastrointestinal Effects**

Chloride is regulated by absorption and secretion in the gastrointestinal tract and reabsorption and excretion by the kidney. Excess chloride induces renal vasoconstriction through reabsorption and tubuloglomerular feedback, decreasing glomerular filtration rate and renin activity, whereas increasing responsiveness to angiotensin II (14). These effects reduce renal blood flow, diuresis, and natriuresis. Chloride may also cause thromboxane release and increased responsiveness to circulating vasoconstrictors (15).

A 2012 study in healthy volunteers demonstrated sustained hyperchloremia after .9% saline infusion associated with reduced renal blood flow and reduced renal cortical tissue perfusion. Infusion of Plasmalyte was not associated with these changes. Also, whereas blood volume changes were identical, a greater subsequent expansion of the extravascular fluid compartment was observed with saline infusions (16). In a small study of elderly patients undergoing major surgery, infusion of saline solution (or 6% HES in saline solution) versus balanced solution (or 6% HES in a balanced solution) was associated with a more prolonged time to first micturition, significant metabolic acidosis, and worsened gastric mucosal tonometry (17). A study of 1407 intensive care patients treated with either a chloride-liberal or a chloride-restrictive strategy demonstrated a significant increase in acute kidney injury (AKI) as defined by the RIFLE (Risk, Injury, Failure, Loss, ESRD) criteria and in the use of renal replacement therapy (RRT) in the chloride-liberal group. No mortality differences were demonstrated (18). Finally, a large observational study of 30,994 patients undergoing abdominal surgery who received either .9% saline or a balanced crystalloid solution demonstrated increased morbidity with the use of .9% saline with increased infection risk, increased AKI, and requirement for RRT and increased requirement for blood transfusion (19).

### **Infection**

Hyperchloremia is associated with proinflammatory and procytokine effects (14). In patients with hyperchloremia, altered immune responses may increase the risk of infection. Also, acute kidney injury and RRT increase infection risk.

### **Coagulation and Bleeding Effects**

In high doses, .9% saline may cause coagulopathy (19). Mechanisms contributing to this include dilution, acidosis, and the absence of calcium within the saline solution (14). Clinical studies are limited and no difference in bleeding or blood product use has been consistently demonstrated.

### **Colloids**

Some studies have reviewed colloids in balanced versus saline solutions. In a 2006 study of 81 patients undergoing cardiac surgery, HES in a balanced solution or normal saline was administered with comparison of total volumes required, serum pH, serum chloride, and base excess levels. No differences in volume of fluid required were noted between groups. Lower chloride levels and corresponding higher pH and base excess levels occurred in the group administered HES in a balanced solution carrier. No morbidity or mortality outcomes were measured in this study, however (20).

### **Future Research**

Further large randomized trials are warranted to examine the incidence and effects of hyperchloremia in hospitalized patients and patient subgroups such as cardiac surgery. The chloride content is not the only difference between .9% saline and balanced crystalloids, and the possible beneficial effects of buffers or lactate should also be studied.

### **Conclusions**

Recent research is consistent in demonstrating possible harm with the use of .9% saline versus balanced crystalloids in fluid therapy. The exact mechanisms and extent of possible harm are not fully elucidated, and more research is likely to be beneficial.

## **BALANCE IN DOSES: RESTRICTIVE VERSUS LIBERAL ADMINISTRATION**

Fluid therapy is often used to achieve hemodynamic targets such as cardiac output, mean arterial blood pressure, and central venous pressure; however, overadministration of fluid may be as harmful as inadequate fluid resuscitation. The optimum hemodynamic targets for achieving end-organ perfusion are still not known, are likely to vary between patients, and may vary over time for an individual patient. Excess fluid may impair tissue oxygenation, wound healing, and is associated with AKI (21).

The Fluid Expansion As Supportive Therapy (FEAST) trial compared bolus fluid resuscitation (saline or albumin) with standard slow rehydration therapy in more than 3000 children in sub-Saharan Africa presenting to the hospital with severe infections. The trial demonstrated increased mortality with fluid bolus therapy with either saline or albumin when compared with standard rehydration (22). In contrast, studies of early goal-directed therapy have demonstrated improved outcomes including reduced mortality with fluid bolus therapy directed by hemodynamic targets and protocolized treatment pathways (23).

Several trials are currently in progress examining optimal fluid dosing and timing regimens (e.g., REstrictive versus LIbEral Fluid therapy in major abdominal surgery [RELIEF] trial).

## SUMMARY

Current evidence suggests that there is no benefit, but significant harm, associated with the use of synthetic colloid solutions as intravenous fluids. Because synthetic colloid solutions also have increased cost compared with crystalloid solutions, their continued use cannot be justified. The use of albumin remains controversial and in most clinical circumstances offers no benefit over crystalloid solutions. However, albumin use may be appropriate in clinical circumstances where even small differences in fluid balance are important for patients or in patients with severe sepsis.

There is increasing evidence in favor of the use of balanced crystalloid solutions rather than isotonic saline with reduced metabolic acidosis and reduced AKI in patients treated with balanced crystalloid versus isotonic saline solutions. Large randomized controlled trials are needed to confirm the benefits of balanced solutions over normal saline.

Not only is the type of fluid administered clinically relevant, but the dose of fluid is likely to contribute to clinical outcomes with excess fluid administration associated with increased tissue edema, coagulopathy, acidosis, hemodilution, and potential organ dysfunction, whereas inadequate fluid resuscitation may be associated with inadequate cardiac output and organ perfusion with resultant dysfunction. No single method for determining appropriate fluid dose and targets for resuscitation exists currently with clinical markers of adequate resuscitation and monitoring adjuncts used most commonly.

Overall, this author advocates careful consideration of the indication for fluid administration, any potential contraindications and adverse effects that may be associated with a particular fluid, and consideration and careful monitoring of the resuscitation targets for any individual patient.

## REFERENCES

1. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med.* 2012;367:1901–11.
2. SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med.* 2004;350:2247–56.

3. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilisation after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. *Ann Surg.* 2012;255:821–9.
4. Maitland K, Kiguli S, Opoka R, et al. Mortality after fluid bolus in African children with shock. *N Engl J Med.* 2011;364:2483–95.
5. Guidet B, Soni N, Della Rocca G, et al. A balanced view of balanced solutions. *Crit Care.* 2010;14:325.
6. Raghunathan K, Shaw AD, Bagshaw SM. Fluids are drugs: Type, dose and toxicity. *Curr Opin Crit Care.* 2013;19:290–8.
7. Becker BF, Chappell D, Bruegger D, et al. Therapeutic strategies targeting the endothelial glycocalyx: Acute deficits, but great potential. *Cardiovasc Res.* 2010;87:300–10.
8. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med.* 2012;367:124–34.
9. Skhirtladze K, Base EM, Lassnigg A, et al. Comparison of the effects of albumin 5%, hydroxyethyl starch 130/0.4 6%, and Ringer's lactate on blood loss and coagulation after cardiac surgery. *Br J Anaesth.* 2014;112:255–64.
10. Mathew JP, Burkhard Mackensen G, Phillips-Bute B, et al. Effects of extreme hemodilution during cardiac surgery on cognitive function in the elderly. *Anesthesiology.* 2007;107:577–84.
11. Reinhart K, Perner A, Sprung CL, et al. Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. *Intensive Care Med.* 2012;38:368–83.
12. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med.* 2013;41:580–637.
13. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev.* 2013;2:CD000567.
14. Mohd Yunus N, Bellomo R, Story D, et al. Bench-to-bedside review: Chloride in critical illness. *Crit Care.* 2010;14:226.
15. Quilley CP, Lin YS, McGiff JC. Chloride anion concentration as a determinant of renal vascular responsiveness to vasoconstrictor agents. *Br J Pharmacol.* 1993;108:106–10.
16. Chowdhury AH, Cox EF, Francis ST, et al. A randomised, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and Plasma-Lyte 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg.* 2012;256:18–24.
17. Wilkes NJ, Woolf R, Mutch M, et al. The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. *Anesth Analg.* 2001;93:811–6.
18. Mohd Yunus N, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA.* 2012;308:1566–72.
19. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization after open abdominal surgery. *Ann Surg.* 2012;255:821–9.
20. Base E, Standl T, Mahl C, et al. Comparison of 6% HES 130/0.4 in a balanced electrolyte solution versus 6% HES 130/0.4 in saline solution in cardiac surgery. *Crit Care.* 2006;10(Suppl 1):176.
21. Kambhampati G, Ross EA, Alsabbagh MM, et al. Perioperative fluid balance and acute kidney injury. *Clin Exp Nephrol.* 2012;16:730–8.
22. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med.* 2011;364:2483–95.
23. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345:1368–77.