Isotonic and hypertonic crystalloid solutions in the critically ill

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Disorders of fluid and electrolyte balance in the critically ill are volume-related, compositional, or both. Targeting ‘normal’ values for plasma volume, osmolality and electrolytes might not be optimal in conditions as diverse as intracranial trauma/haemorrhage, hepatic encephalopathy, abdominal hypertension, or major surgery, because a hyperosmolar state seems to favourably affect tissue (brain and intestinal) oedema formation. However, adequately powered studies regarding the impact of hypertonic saline on outcome are lacking. Isotonic crystalloids are the cornerstone of resuscitation and must be balanced against natural or artificial colloids and vasopressors. Crystalloid resuscitation is superior to vasopressors in shock associated with blunt trauma, and is at least not inferior to colloids in septic shock. Traditional rules of thumb indicating the need for three to four times the amount of crystalloids for the plasma volume to be replaced are probably erroneous and might have contributed to association of overly aggressive crystalloid resuscitation with poor outcome.

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The Yin and Yang of early ‘aggressive’ resuscitation with crystalloids

A positive fluid balance is associated with morbidity and mortality in otherwise uncomplicated major elective surgery.1 In the critically ill, effects of surgery per se and its associated changes in the...
hormonal milieu interne are exaggerated by a systemic inflammatory response with development of capillary leak (Fig. 1). This leads to difficult-to-balance losses into the interstitium and frequently visible oedema formation. Resulting abnormalities of fluid and electrolyte balance in the critically ill are purposefully or involuntarily influenced, in addition, by nutritional support and measures that affect acid–base homeostasis.

Crystalloid resuscitation should be targeting a ‘corridor of safety’, avoiding both extremes of overt hypovolaemia and fluid overload. While avoidance of oedema formation is a prime objective and concern in visceral surgery, efforts to restrict fluids, such as ‘forced hypovolaemia’, are associated with oliguria and occasionally renal shutdown, and may impair nutritional microvascular blood flow in other vascular beds such as the splanchnic circulation. Fluid excess, on the other hand, is presumably a cause of perioperative morbidity and mortality. Sequelae of volume overload are particularly well known, and the pathophysiological cascades of events have been worked out best for the patient with aggressive crystalloid resuscitation after major trauma: Manifestations of crystalloid overload might include acute respiratory distress syndrome (ARDS) and brain oedema in the patient with concomitant head injury. Lately, development of secondary abdominal compartment syndrome (ACS) has claimed attention, i.e. ACS in the absence of abdominal injury which is associated frequently with haemorrhagic shock and early and excessive crystalloid resuscitation. In a recent trial in patient cohorts with severe extremity injuries in the absence of abdominal trauma, obtained from the Trauma Registry of the American College of Surgeons database, patients developing secondary ACS had significantly higher operating-room crystalloid administration (9.9 L versus 2.7 L), more frequent use of a rapid-infusing system (12.5% versus 0.0%), and multiple logistic regression identified early crystalloids as predictors of secondary ACS. On the other hand, a prospective trial comparing resuscitation

Fig. 1. Changes in the neurohumoral milieu interne and pathophysiological factors affecting blood volume, fluid balance and electrolytes in the critically ill surgical patient. While presumably adaptive changes regarding neurohumoral axes will occur even in uncomplicated major surgery, the systemic inflammatory response complicates pathophysiology in particular in supervening nosocomial infection and sepsis and concomitant organ failure. SIRS, systemic inflammatory response system; MODS, multiple organ dysfunction syndrome; ADH, antidiuretic hormone.
with normal saline, 4% gelatine, 6% hydroxyethyl starch (HES) 200/0.5 and 5% albumin in 67 ICU patients with acute lung injury after cardiac or major vascular surgery showed that the type of fluid did not affect pulmonary permeability and oedema. The concept of interstitial overloading as a result of overly aggressive crystalloid resuscitation with its sequelae has led to a renewed interest in the use of vasopressors as an adjunct or even an alternative to crystalloid resuscitation after major injury. A recent multicentre prospective cohort study evaluated outcomes of blunt-injured adults with haemorrhagic shock receiving vasopressors (norepinephrine, phenylephrine, dopamine, or vasopressin) or ‘aggressive’ early crystalloid resuscitation with mortality as primary endpoint. Cox proportional hazard regression controlling for important physiological, injury, and demographic confounders revealed that vasopressor use within 12 hours after injury was independently and significantly associated with higher risk of mortality (hazard ratio 1.81, 95% confidence interval [CI] 1.1–2.9, \( P = 0.013 \)), and a twofold higher risk of mortality at 24 hours (HR 2.15, 95% CI 1.4–3.4, \( P = 0.001 \)) independently of the individual vasopressor used. As a result, early use of vasopressors for haemodynamic support after haemorrhagic shock cannot replace early crystalloid resuscitation after severe blunt injury and is independently associated with unfavourable outcome. Thus, both under-resuscitation with ‘vasopressor-masked hypovolaemia’ as well as ‘inundation’ with crystalloids is deleterious for victims of blunt trauma, a concept which might be applicable for other types of shock and critical illness in general as well.

### How to assess the ‘corridor of safety’ for crystalloid resuscitation?

Diagnosis and therapy of disturbances in the fluid and electrolyte homoeostasis are traditionally based on haemodynamic parameters such as (filling) pressures and measurements of electrolytes and acid–base chemistry in the intravascular compartment, which amounts to approximately 25% of extracellular fluid, and in turn represents only 34% of total body water. As such, both hypo- and hypervolaemia are not easily appreciated, and ‘normal’ values per se might not be appropriate for various patient cohorts, such as those presenting with intracranial or intra-abdominal hypertension, ARDS, as well as cardiac failure or comorbidity. Haemodynamic variables that differentiate the patterns of survivors from non-survivors of circulatory shock have been used to develop diagnostic and therapeutic goals. Although a matter of continuing debate, colloids (either albumin or artificial colloids such as HES and gelatine) are preferred over crystalloids for reasons of practicability and theoretical considerations regarding plasma osmolality and oedema formation, mainly because three to four times the amount of isotonic crystalloids have been traditionally suggested to be needed to replace a suspected deficit in the intravascular compartment.

Despite these widely accepted general considerations regarding guidance of volume support and impact on clinical outcome, data from large clinical studies in various populations of critically ill patients cast doubt on these paradigms, both regarding guidance of volume support as well as the choice of fluids.

### Haemodynamic endpoints for resuscitation

The ultimate goal of resuscitation in shock is to restore the balance between oxygen demand and delivery, yet typically filling pressures rather than oxygen transport variables are monitored to define resuscitation endpoints in the critically ill.

The use of pulmonary artery catheters (PACs) has been a source of controversy and is thought by many practitioners to be useful in those patients presenting problems regarding the ‘Yin-Yang’ of volume loading. Acute lung injury and ARDS are prime examples of this pathophysiology. The ARDS clinical trials network has recently conducted a risk–benefit analysis of PACs in 1000 patients with established acute lung injury in a randomized trial comparing haemodynamic management guided by a PAC versus central venous catheters (CVCs) using an explicit management protocol with mortality as the primary outcome. Rates of death during the first 60 days before discharge home were similar in the PAC and CVC groups as were ventilator-free days as a surrogate for improvement of lung function. Interestingly, PAC-guided therapy did not improve these measures in the subgroup of patients in shock at the time of enrolment. Furthermore, there were no significant differences between groups in lung or kidney function, rates of hypotension, ventilator settings, or use of dialysis or vasopressors.
balance was similar in the two groups, as was the proportion of instructions given for fluid and diuretics. This study, and various others not discussed in detail here, cast doubt not only on the use of PACs in ARDS, but more generally raise the question of what parameters are appropriate to guide (crystalloid) resuscitation or define the safety margin of volume loading. Similarly, research is warranted to define the role of ‘dynamic’ preload parameters derived from heart–lung interaction in the respiratory cycle.

Hydrostatic pressure, oncotic pressure and the Starling equation: options and deceptions

Even under physiological conditions capillaries behave like leaky hosepipes where a balance of hydrostatic versus oncotic pressure, as described by the Starling equation, determines the net filtration rate. While in healthy subjects most of the fluid stays inside the pipe, approximately 20 L are filtered into the extravascular space each day, of which 16 L re-enter the circulation. These continuous exchange processes are likely to be exaggerated under conditions of shock and sepsis, with energetic failure and impairment of ion pumps and direct injury to the cells of the vessel wall, also referred to as ‘capillary leak syndrome’. The goal of fluid resuscitation is to restore the circulating blood volume, which in the critically ill includes substitution of external and internal losses, including interstitial fluid accumulation and supplying volume to a dilated vascular system as in the case of sepsis. This goal must be achieved within the very early phase of critical illness also referred to as the ‘golden hour of shock’.

As time is of the essence, favourable pharmacodynamic data for colloids compared to crystalloids has led to the general concept of superiority of colloids over crystalloids to restore macro- and microcirculation in a timely fashion, along with less oedema formation due to their oncotic properties. Challenging this paradigm against published evidence casts substantial doubt on the validity of the pharmacodynamic data (obtained in healthy individuals or based on theoretical calculations of the various fluid spaces) under conditions of critical illness. Some recent randomized controlled trials (RCTs) have addressed these fundamental issues of controversy in intensive care over the last decade.

When septic patients with values of CVP, central venous oxygen saturation (ScvO2) and mean arterial blood pressure (MAP) below target were resuscitated with hyperoncotic HES or modified Ringer’s, only CVP returned to target more quickly after HES ($P = 0.003$), while ScvO2 and MAP normalized equally fast with crystalloid. Even more worrisome, children with Dengue shock syndrome who received colloids achieved initial cardiovascular stability more rapidly and showed a faster reduction in median haematocrit values during the first 2 hours (25%, 22% and 9% reduction for dextran, gelatine and Ringer’s, respectively; $P < 0.001$). Subsequently, however, their haematocrit increased more than with Ringer’s (5% increase for dextran or gelatin, 0% for Ringer’s; $P < 0.001$). The authors explained this as a combination of fluid effects and vascular leak. In other words, colloids exerted a short-lived intravascular volume effect followed by a rebound increase in vascular leak after a few hours. As a consequence, overall time to final stabilization was not different between groups. Thus, these data lend support to the concept that in the case of an impaired endothelial barrier in systemic inflammation, colloids are not retained in the intravascular space and may even after their sequestration generate increased oncotic pressure in the interstitium, with subsequent fluid accumulation.

The crystalloid versus colloid controversy: has the fat lady sung?

Data to support the choice of either crystalloids or artificial and natural colloids in the critically ill are tipping the scales toward crystalloids for reasons of safety, side effects and containment of costs. The data from the Saline versus Albumin Fluid Evaluation (SAFE) study, a multicentre, randomized, double-blind trial to compare the effect of fluid resuscitation with albumin or saline on mortality in a heterogeneous population of patients in the ICU, were reported in 2004, and subgroup analyses on patients with traumatic brain injury and interference with baseline albumin concentration have been reported since. In this study, almost 7000 patients who had been admitted to the ICU were randomly assigned to receive either 4% albumin or normal saline for intravascular-fluid resuscitation,
with death from any cause during the 28-day period after randomization as the primary outcome measure. No differences were observed regarding either the primary endpoint (relative risk of death, 0.99; 95% CI, 0.91–1.09; *P* = 0.87) or the secondary endpoint (development of new single-organ and multiple-organ failure). A detailed subgroup analysis in 460 patients with history of traumatic brain injury confirmed the crude analysis in the initial study regarding unfavourable effect of albumin in those patients. At 24 months, in the albumin group 33.2% as compared to 20.4% of patients in the saline group had died (relative risk, 1.63; 95% CI, 1.17–2.26; *P* = 0.003).

The outcomes of resuscitation with albumin and saline were similar irrespective of patients’ baseline serum albumin concentration, suggesting that saline was safe even in those patients starting off with a low albumin upon admission. A synoptic view of these well-designed RCTs addressing either natural (SAFE) or artificial (VISEP) colloids revealed, unexpectedly, that the perceived advantages of colloids (faster resuscitation and several-fold lower volume load) passed on over generations of ICU practitioners may have been overrated: Required crystalloid-to-colloid volume ratios ranged between 1.3 and 1.7, possibly due to vascular leakage in critically ill patients. Furthermore, while 4% albumin was safe except in patients with traumatic brain injury, the artificial colloid HES studied in the VISEP study has dose-dependent detrimental side-effects on kidney function, coagulation and overall mortality.

**Isotonic as opposed to hypertonic crystalloids: can less be more?**

While evidence is solidifying to support the use of crystalloids over colloids in the critically ill, the question regarding composition and concentration of salts in crystalloid formulations arises. This review addresses aspects of crystalloid resuscitation in general, while readers interested in the specific impact of balanced salt solutions as opposed to normal saline, i.e. differences in chloride load and their impact on acid–base balance, are referred to recent reviews. As discussed earlier, use of hypertonic salt solutions might affect the fluid balance in general in a favourable way and might specifically reduce intracranial pressure (ICP). A single equimolar infusion of 7.45% hypertonic saline solution is as effective as 20% mannitol in decreasing ICP in patients with brain injury. However, in a recent study by Francony and co-workers, mannitol exerted additional effects on brain circulation through a possible improvement in blood rheology. The authors propose to consider factors, such as serum sodium, systemic haemodynamics, and brain haemodynamics when deciding on use of either mannitol or hypertonic saline solution for patients with increased ICP. In the light of these and other data, mannitol remains the first-line drug in intracranial hypertension of various origins, but hypertonic saline is an interesting rescue option to improve cerebral perfusion. For instance, in patients with poor-grade subarachnoidal haemorrhage, bolus systemic hypertonic saline therapy led to dose-dependent increments of cerebral blood flow and was able to restore normal perfusion. Similarly, recent guidelines for management of acute liver failure with higher grades of hepatic encephalopathy herald initial therapy with mannitol if intracranial pressure equals or exceeds 25 mmHg, supplemented if insufficient by hypertonic saline: Specifically, serum sodium should be maintained at least within high normal limits, and hypertonic saline administered to 145–155 mmol/L may be considered in patients with intracranial hypertension refractory to mannitol.

Although pathophysiologically reasonable, data to support similar effects in body cavities other than the intracranial compartment are scarce but reflect an area of active research. Although the molecular mechanisms for the proposed beneficial actions of hypertonic solutions have not been worked out sufficiently, mechanisms beyond the reduction of tissue oedema via influence on the Starling equation have been advocated, such as direct actions on innate immunity.

Hypertonicity seems to affect some innate immune-cell functions, specifically neutrophil burst activity in preclinical studies, but the clinical significance remains controversial. In a recent double-blind study, 15 women scheduled for open abdominal hysterectomy were randomized to infusion of 4 mL/kg 7.5% NaCl, 4 mL/kg 0.9% NaCl, or 32 mL/kg 0.9% NaCl over 20 minutes, with determination of leukocyte and differential counts, neutrophil endothelial adhesion molecule expression, and oxidative burst as read-out parameters. In contrast to laboratory data, the well-established effect of elective surgery per se, i.e. reduced expression of adhesion molecules and
superoxide production, was not affected by the hypertonic saline preparations in elective abdominal surgery.\textsuperscript{50} In a similarly weakly powered study in 27 patients admitted with haemorrhagic shock due to trauma, a single bolus (250 mL) of either 7.5% NaCl/6% dextran-70 or isotonic NaCl was administered and changes in immune/inflammatory markers were monitored. Hyperosmolarity was modest and transient, whereas some immunological/anti-inflammatory effects persisted over the first day. Hypertonic saline/dextran affected polymorphonuclear neutrophils, i.e. blunted shock-induced CD11b up-regulation, and was associated with CD62L shedding. Similarly, it altered the inflammatory phenotype of monocytes with consistent reduced pro-inflammatory (tumour necrosis factor) and increased anti-inflammatory (IL-1ra and IL-10) cytokine profiles.\textsuperscript{51}

Based on these concepts and data, the hypothesis that blunting of a dysfunctional inflammatory response will reduce organ failure and presumably lead to reduction in ARDS was tested in a double-blind RCT with pre-hospital enrolment after major trauma. The study was stopped for futility after the second interim analysis after enrolment of 209 patients (110 in hypertonic saline/dextran and 99 in the lactated Ringers group) and intent-to-treat analysis demonstrated no significant difference in ARDS-free survival (hazard ratio 1.01; 95% CI 0.63–1.60). Nevertheless, improved ARDS-free survival in a subset of patients requiring 10 units or more of packed red blood cells (hazard ratio 2.18; 95% CI 1.09–4.36) would be consistent with a benefit in patients at highest risk of ARDS.\textsuperscript{52} Although the authors attribute potential benefit to possible effects on innate immunity, a simple effect via reduced requirements of fluids along with less oedema formation, with possible favourable effects on extravascular lung water as well as intra-abdominal compartment pressures, cannot be ruled out.

Consistent with the latter, recent evidence would also support the idea that hypertonic resuscitation can attenuate extravascular lung water and secondary abdominal compartment syndrome as a highly lethal complication in another patient population, i.e. patients being resuscitated from burn shock. Traditional resuscitation according to the Parkland formula is a prime example for the traditional concept of high-volume ‘aggressive’ crystalloid resuscitation. A recent study analysed patients with burns ≥40% of the total body surface area without severe inhalation injury which were entered into a fluid resuscitation protocol using hypertonic saline (n = 14) or lactated Ringer’s solution (n = 22). Urine output was monitored hourly, with a goal of 0.5–1.0 mL/kg per hour. Haemodynamic parameters, blood gas analysis, intra-bladder pressure as an indicator of intra-abdominal pressure (IAP), and the peak inspiratory pressure were recorded. In the hypertonic saline group, the amount of intravenous fluid volume needed to maintain adequate urine output was less at 3.1 ± 0.9 versus 5.2 ± 1.2 mL/24 h per kg per percentage of total body surface area, and the peak intra-abdominal and inspiratory pressures at 24 hours after injury were significantly lower than those in the lactated Ringer’s group. While 14% of patients receiving hypertonic resuscitation developed intra-abdominal hypertension during the first day, this rate was 50% for isotonic resuscitation.\textsuperscript{53}

A consistent observation regarding a potential beneficial effect of hypertonic saline against oedema formation was reported for a different patient cohort, i.e. children undergoing open-heart surgery for atrial or ventricular septal defects. In a controlled, randomized, blinded study to assess efficacy and safety of a hypertonic–hyperoncotic solution, children were randomly assigned to receive 7.2% sodium chloride with 6% HES or 0.9% sodium chloride (n = 25 each). In the group receiving hypertonic–hyperoncotic resuscitation, cardiac index increased by 64% upon administration of the study solution and returned to pre-values only after 4 hours, while isotonic saline was largely without effect on these studied parameters. In parallel, extravascular lung water index decreased from 10.6 ± 1.2 to 5.6 ± 1.2 mL/kg, while it increased with isotonic saline from 12.3 ± 1.1 mL/kg to 18.1 ± 1.7 mL/kg immediately upon administration, remaining elevated for 60 minutes after volume loading (15.6 ± 1.5 mL/kg). Catecholamine requirements were lower, and a positive inotropic along with a decrease in peripheral resistance was observed.\textsuperscript{54}

**Conclusions and future directions**

Significant progress has been made in the last few years with respect to the understanding of basic principles of volume resuscitation in the critically ill. Isotonic crystalloids are safe and effective for use in the critically ill, and the amount of crystalloid required to restore circulating blood volume is substantially less than assumed in the past. Hypertonic saline offers some potentially interesting
aspects with respect to tissue oedema and fluid balance. Adequately powered RCTs are warranted to define the role of these theoretical benefits with respect to outcome.\textsuperscript{55}

**Practice points**

- isotonic crystalloids are non-inferior to albumin in a general population of critically ill patients, while some patient groups (such as those with traumatic brain injury) might benefit from iso- and/or hypertonic saline
- isotonic crystalloids reflect the cornerstone of volume resuscitation in the critically ill and are probably superior to artificial colloids in the septic patient
- care should be taken to avoid overload by crystalloids; adequate volume support can be achieved with less isotonic crystalloids than assumed in the past, and while crystalloid-to-colloid ratios of approximately 3 have been advocated, a ratio of approximately 1.5 is closer to reality
- when monitoring fluid loading to restore blood volume, parameters of oxygen transport and dynamic preload assessment should be considered, and fluid intake should be limited to avoid excess volume
- alarm parameters for overt fluid overload might include CVP, IAP, and extravascular lung water
- hypertonic formulations might offer benefits with respect to tissue oedema formation, fluid balance, and intracranial or intra-abdominal compartment syndrome
- mannitol is the first-line drug for osmotherapy in intracranial hypertension, but hypertonic saline is an interesting adjunct in cases in which elevated intracranial pressure is not sufficiently controlled by mannitol

**Research agenda**

- although fluid therapy is a most basic measure with overt impact on outcome, knowledge on required volumes as well as their optimal composition is surprisingly sparse in the critically ill
- research is warranted regarding surrogate endpoints for crystalloid loading, such as parameters derived from oxygen transport (e.g. ScvO\textsubscript{2}), heart–lung interaction, extravascular lung water formation, and intra-abdominal pressure to define a ‘corridor of safety’
- differential aspects of isotonic as opposed to hypertonic salt solutions and their impact on outcome in various disease entities remain to be determined; this includes aspects of safety and efficacy, e.g. regarding optimal saline concentration, and their potential side-effects e.g. on brain or kidney, as well as impact of the respective inorganic or organic anions used

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