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Adverse effects of crystalloid and colloid fluids

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Abstract

Guidelines for infusion fluid therapy rarely take into account that adverse effects occur in a dose-dependent fashion. Adverse effects of crystalloid fluids are related to their preferential distribution to the interstitium of the subcutis, the gut, and the lungs. The gastrointestinal recovery time is prolonged by 2 days when more than 2 litres is administered. Infusion of 6–7 litres during open abdominal surgery results in poor wound healing, pulmonary oedema, and pneumonia. There is also a risk of fatal postoperative pulmonary oedema that might develop several days after the surgery. Even larger amounts cause organ dysfunction by breaking up the interstitial matrix and allowing the formation of lacunae of fluid in the skin and central organs, such as the heart.

Adverse effects of colloid fluids include anaphylactic reactions, which occur in 1 out of 500 infusions. The possibility that hydroxyethyl starch causes kidney injury in patients other than those with sepsis is still unclear. For both crystalloid and colloid fluids, coagulation becomes impaired when the induced haemodilution has reached 40%. Coagulopathy is aggravated by co-existing hypothermia. Although oedema can occur from both crystalloid and colloid fluids, these differ in pathophysiology.

To balance fluid-induced adverse effects, this review suggests that a colloid fluid is indicated when the infused crystalloid volume exceeds 3–4 litres, plasma volume support is still needed, and the transfusion of blood products is not yet indicated.

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STRATEGIES FOR VOLUME REPLACEMENT

Three approaches may be taken for volume replacement by infusion fluids during surgery and intensive care.

1. **Fluid balance method.** This means that perceived needs and losses are summarized continuously and that the volume is substituted with crystalloid and colloid fluid in proportion to their respective plasma volume-expanding properties. The summary method is old but remains the main approach used worldwide.
2. **Outcome-guided method.** Fluid is given as suggested by randomized clinical trials that compare surgical complications after the use of different fluid programs. The outcome-oriented approach has been used for 15 years. Most data pertain to open abdominal surgery.
3. **Goal-directed fluid therapy.** Here, fluid volume is administered with the aim of reaching a pre-determined hemodynamic target. Most commonly, colloid fluid is given as bolus infusions until the each heartbeat pumps less than 10% more than before the last bolus [1]. Although crystalloid fluid has been proposed as an alternative, it lacks a pharmacokinetic basis, as crystalloids have a marked distribution phase whereby 50% of the volume effect is lost within 30 minutes [2]. While goal-directed fluid therapy was developed in the 1980s, it was popularized for perioperative use at the beginning of this millennium.

Arterial pressure, central venous pressure, and urinary excretion only give vague signals about inappropriate fluid

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therapy. Although central venous pressure rises when the volume of administered fluid has clearly passed the flat portion of the Frank Starling curve [3], the venous pressure may also be affected by other stimuli. Arterial pressure and urinary excretion indicate underhydration, but only at a very late stage.

ROLE OF FLUID

One might wonder why fluid is needed at all during surgery, apart from the mandatory replacement of blood loss to avoid gross hypovolemia. Evaporation from open wounds is now accepted to be smaller than believed in the past, with a evaporation rate of 35 mL h^{-1} during major abdominal surgery [4]. Moreover, the preoperative evaporation of body water overnight amounts to only a few hundred millilitres.

Perhaps a more important concern is that as general anaesthesia disrupts the normal autonomic control of the circulation, it then can be said to induce a mild form of distributive shock. Blood is directed away from the gastrointestinal tract, which is an early trouble-spot for ischemia. A review by Apfel *et al.* [5] showed that the administration of as little as 2 mL kg^{-1} h^{-1} of crystalloid fluid during surgery was associated with a higher incidence of nausea, which may be due to this type of re-distribution. An additional infusion of crystalloid fluid alleviated the problem, thereby supporting local hypovolemia as the cause.

The current recommendation is to provide 3–5 mL kg^{-1} h^{-1} of crystalloid fluid during ongoing surgery, although more fluid should be given in cases where blood loss is more than minimal. A volume kinetic simulation of crystalloid fluid administration in this range shows that a plasma volume expansion of between 50 and 170 mL may be expected after 3 hours of surgery (Fig. 1). These calculations are based on previous data obtained during thyroid surgery [6]. They are clear of the effects of blood loss, but not of evaporation. No steady state develops due to the slow rate of elimination of crystalloid fluid during anaesthesia and surgery. However, with the 3 mL kg^{-1} h^{-1} fluid support option, a bolus infusion of 300 mL, given over 10 min at the onset of the anaesthesia, will achieve an early plasma volume expansion of 100 mL and maintain it at a fairly constant level over many hours. The 5 mL kg^{-1} h^{-1} option will always produce some progressive accumulation of fluid, which, as suggested by the kinetic analysis, accounts for blood loss of up to 100 mL.

GENERAL ADVERSE EFFECTS

Acute hemodynamic overload. In conscious patients with a poor cardiac reserve, a brisk infusion of infusion fluid might precipitate pulmonary oedema. During general anaesthesia, this acute hemodynamic overload is indicated by a sharp rise in central venous pressure and, naturally, by an absence of fluid responsiveness. The central venous pressure is expected to remain unchanged as long as the patient is fluid responsive [3].

Body temperature. Fluids infused at room temperature promote hypothermia by increasing the conductive heat loss. This may cause thermal discomfort and shivering during postoperative care. Moreover, a larger blood loss due to coagulopathy may be expected if the body temperature falls to 35°C and below. Useful preventative measures include the use of blankets to cover the body and warming of the infusion fluids.

Coagulation. All infusion fluids impair coagulation by diluting the plasma proteins. As infusion fluids distribute only over the plasma volume, the dilution of the plasma proteins will be about twice as great as the haemodilution. However, crystalloids (and possibly gelatine) actually strengthen the coagulation until the blood has been diluted by 40%, after which coagulopathy develops. The coagulation effect is best assessed by measuring the plasma fibrinogen concentration, which should not drop below 1 g L^{-1} (normal range 1.5–3.0 g L^{-1}). The haemostatic problems worsen and may even become uncontrollable if dilution coagulopathy co-exists with hypothermia.

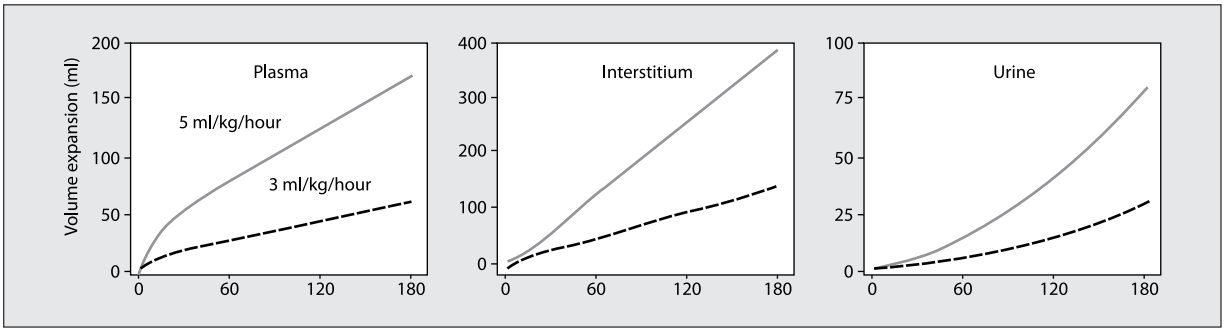

Figure 1. The volume expansion of the plasma, interstitium, and urine when Ringer´s acetate solution is infused at 3 mL kg^{-1} h^{-1} and 5 mL kg^{-1} h^{-1} during general anaesthesia. Computer simulation was based on volume kinetic data derived from thyroid surgery [6]. The mean body weight of the studied patients was 69 kg, meaning that a total of 620 mL and 1,035 mL were infused over 3 hours. A few hundred ml could not be detected in the kinetic system, as discussed elsewhere (see [7]), and this probably represents evaporation and the formation of lymph

Pain. Hypertonic fluids often cause pain due to local inflammation at the site of infusion, which may cause thrombophlebitis. A large vein should be used for lengthy infusions if the osmolality of the fluid exceeds 600 mosmol kg^{-1}.

ADVERSE EFFECTS OF CRYSTALLOID FLUIDS

Adverse effects of crystalloid fluids are usually unrelated to acute plasma volume expansion but instead are related to their preferential distribution to specific interstitial areas. These are the subcutis, the gastrointestinal tract and the lungs.

Isotonic, or nearly isotonic crystalloid fluids are harmless up to a volume of 2 L. However, if infused over as short time as 15 min, this volume causes uncomfortable transient sensations of swollenness in the trunk and face, and even dyspnoea [8].

The first clinical consequence when administrating more than 2 litres of fluid is a delay in the gastrointestinal recovery time of 2 days [9]. However, the total number of postoperative complications still seems to be lowest when providing between 1.75 and 2.75 L of crystalloid fluid during open abdominal surgery [10].

Increasing the crystalloid fluid load to 6–7 L in colon surgery increases the risk of wound infection, suture insufficiency, bleeding, pulmonary oedema, and pulmonary infection [11]. These fluid volumes are associated with a weight increase of several kilos, which may persist for 4–5 days postoperatively. Providing even more fluid increases the risk of fatal pulmonary oedema, which may occur several days after the surgery [12].

Old age and low arterial pressure restrict the elimination of fluid during the actual surgical procedure, thereby promoting fluid overload [13]. A recent review showed that the half-life of crystalloid fluid is as much as 10 times longer during surgery than in conscious volunteers [14]. In contrast to crystalloid fluid delivery during the intraoperative period, a restrictive crystalloid fluid program in the postoperative period does not seem to limit the number of complications [15]. At this stage, fluid appears to be even more readily excreted than before the surgery [16].

Infusion of even larger volumes of crystalloid fluid turns the normal negative interstitial pressure to positive, and lacunae of fluid form in various tissues. This phenomenon is most easily observed as *pitting oedema* in the subcutis of the legs. Worse yet, lacunae break up the cytoarchitecture in essential organs, such as the heart, which causes cardiac dysfunction that may lead to death. The formation of large lacunae in the myocardium has been demonstrated in animals when isotonic saline is used as comparator to overload with urological irrigating fluids [17, 18].

Isotonic saline is a non-physiologic electrolyte fluid that is associated with the causes of fluid-specific adverse effects. These include metabolic acidosis, impairment of kidney function, possibly abdominal pain, and a higher incidence of postoperative complications [19, 20]. These negative effects may be noted when more than 2 L of isotonic saline has been infused. Recent data suggest that the saline-induced reduction of urinary excretion occurs only if the kidneys are set to retain fluid before the fluid therapy is initiated [21].

Glucose solutions are indicated only in special situations, and perhaps only during very lengthy surgery. The body´s capacity to handle glucose infusions is impaired during surgery and at least for several days thereafter. Appropriate rates of infusion are given elsewhere [22]. Glucose solutions should be half-isotonic with regard to electrolytes. Plain glucose may induce subacute hyponatraemia, which presents neurologic disturbances 2–3 days after the surgery [23, 24].

ADVERSE EFFECTS OF COLLOID FLUIDS

Anaphylaxis. All colloid fluids are associated with a risk of allergic reactions, which usually appear soon after the infusion has been initiated. A French multicenter study of almost 20,000 patients indicated an incidence of allergic reactions of 0.35% for gelatine, 0.27% for dextran, 0.10% for albumin, and 0.06% for hydroxyethyl starch (HES); these reactions were considered severe in 20% of the patients [25]. As a rule, one may expect one allergic reaction in 500 infusions. A known allergy to drugs is associated with a three-fold increased risk of an allergic reaction. The most common type of reaction involves a feeling of warmth in the skin, erythema, itching and nausea. More severe reactions consist of varying degrees of arterial hypotension and bronchospasm.

Hyperoncotic colloids may induce pre-renal anuria in dehydrated patients as a rise in the plasma oncotic pressure acts to retain fluid in the glomeruli.

Preparation-dependent effects. Large amounts of **albumin** impose a metabolic burden on the patient, as the macromolecule is split into amino acids that are used as energy or incorporated into new proteins. **HES** may harm the kidney in septic patients, although whether this occurs under other circumstances is unclear. More data on this issue are currently being generated in multicenter studies across Europe comparing HES with a balanced crystalloid solution in major abdominal surgery (the Phoenix Study) and in trauma (the Tethys Study). The risk of anaphylaxis from **dextran** means that an injection of 10 mL of a hapten inhibitor should precede infusion of this colloid. Dextran improves microcirculatory flow and may be used to prevent of thromboembolism [26]. Although **gelatine** is the oldest of the colloid fluids, surprisingly little basic data exists to date regarding its behaviour in the human body. Mild allergic reactions are fairly common and mainly materialize as urticaria or transient fever.

CURRENT CONTROVERSIES

Non-colloid strategy. Reports of acute kidney injury from HES in septic patients have initiated world-wide scepticism against the use of colloid fluids among researchers. Current guidelines in Scandinavia recommend crystalloid fluid if no clear difference in outcome is evident between crystalloids and colloids [27]. The volume-associated adverse effects of crystalloids appear to be overlooked. A more rational choice would be to use to a colloid when the infused crystalloid volume already exceeds 3–4 L, plasma volume support is still needed, and the transfusion of blood products is not yet indicated [2].

The non-colloid strategy is also inconsistent with recommendations for the use of goal-directed fluid therapy in the operating room and intensive care. Virtually all evaluations of this method have been performed using HES for plasma volume expansion. As already stated, using a crystalloid for this purpose lacks support from basic science, as half of the acute plasma expansion from a fluid bolus is lost within 25–30 min [2, 13].

Hypervolemia. Recommending goal-directed fluid therapy is inconsistent with warnings of hypervolemia**,** which may cause shedding of the endothelial glycocalyx layer [28, 29]. The purpose of goal-directed fluid therapy is to expand the cardiac chambers so that the cardiac fibres gain strength, and a reasonable supposition is that atrial natriuretic peptides would be released as a result. However, this author has found no study evaluating shedding or atrial natriuretic peptide concentrations caused by adherence to a goal-directed fluid protocol. Although shedding clearly occurs in inflammatory states and ischemia [30, 31], no firm evidence of shedding caused by fluid-induced hypervolemia in a clinical setting has yet been presented. The tracer technology used in early studies of this phenomenon has been criticized [32] and it remains unclear whether measured plasma concentrations of shedding products should be corrected for plasma dilution [33]. Although doing so is correct if the volume of distribution of these products is limited to the plasma volume, it is erroneous if they distribute over a much larger volume. A recent study found little evidence of shedding in response to an infusion of as much as 25 mL kg^{-1} (about 2 L) of crystalloid fluid over 30 min at the beginning of an abdominal hysterectomy [34]. However, no correction for plasma dilution was made in this report.

Crystalloid oedema. The tendency for fluids to cause peripheral oedema is a topic of great importance but one that is quite difficult to study. One bewildering detail is why crystalloid fluid does not distribute instantly throughout the extracellular space (i.e., between plasma and the interstitium) when the radius of the electrolytes is so small (2 Å) relative to the size of small pores in the capillary wall (40 Å). This process, according to many studies, instead requires 25–30 minutes to be completed.

A second related problem is why the intraoperative fluid overload is not readily excreted after the surgery. As already stated, oedema created during the actual surgery requires several days for elimination [11], while fluid infused postoperatively is eliminated promptly [16]. A new theory based on well-known physiology explains the reason as the viscoelastic properties of the gel matrix of the interstitial space. The matrix offers resistance to volume expansion; thereby restricting fluid movements. However, when marked expansion has already occurred, the matrix loses much of its elastic quality, causing the distributed fluid to remain in the periphery. A recent volume kinetic study in volunteers showed that a crystalloid is more apt to remain in the periphery with a brisk infusion than a slow one [7]. These qualities of the interstitial matrix could explain both the relatively long time required for distribution of crystalloid and the problems of recruiting fluid that has already been distributed.

Colloid oedema. Colloid fluids cause a different type of oedema. Even infused macromolecules other than albumin probably undergo capillary leakage because the plasma volume expansion is much shorter than the half-life of the respective macromolecule in the body [14]. Extravasated colloid molecules attract fluid and need to pass through the lymphatic system to become eliminated. This oedema may slowly cause an imbalance of fluid volumes between the plasma and the interstitium that, despite fluid overload, makes diuretic therapy ineffective and even hazardous.

Although the colloid type of oedema is poorly studied and remains speculative, two small studies from my group cast some light on its effects. The infusion of Ringer´s acetate 2 hours after HES in volunteers was followed by a 50% greater peripheral accumulation of fluid, as well as a smaller urinary excretion, when compared to infusion of Ringer´s acetate alone [35]. The increase in body weight afterward was also greater when a colloid (mean 1.0 kg), rather than a crystalloid (mean 0.4 kg), was used for plasma volume expansion during moderate-sized surgery. While the urinary excretion was slightly larger for the colloid during the actual surgery, it was only twice as large as in the crystalloid group during the postoperative period and up to the next morning [36].

CONCLUSIONS

1. Volume therapy can be managed according to the fluid balance method, the outcome-guided method, or the goal-directed method.
2. One reason why fluid is needed is that anaesthesia disrupts the normal autonomic control of the circulation, whereby redistribution of blood flows may cause local ischaemia.

3. General adverse effects of fluid infusion include acute hemodynamic overload, hypothermia, and dilution coagulopathy.
4. Specific adverse effects of crystalloid fluid include as follows: delayed gastrointestinal recovery time (> 2 L); wound infection; suture insufficiency; bleeding; pulmonary oedema and pulmonary infection (6–7 L); risk of fatal pulmonary oedema (> 7 L); and finally, organ dysfunction caused by the destruction of tissue cytoarchitecture due to the formation of lacunae of fluid in the skin and in organs, such as the heart.
5. Specific adverse effects of colloid fluids include anaphylactic reactions (about 1 of 500 infusions) and, for hydroxyethyl starch, an increased risk of kidney injury in septic patients.
6. Although peripheral oedema is caused by both crystalloid and colloid fluids, they have different pathophysiologies and time spans.

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