Crystalloids versus Colloids

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The emotional debate around infusion therapy is ongoing and very often narrowed down to the question whether we should use crystalloids or colloids in general. This simplification, however, is not justified as it ignores the respective distribution behaviours of these two completely different classes of preparations. While isotonic crystalloids have been shown in human patients to remain by only 20% within the circulatory compartment after intravenous infusion, iso-oncotic preparations of hydroxyethyl starch or human albumin almost completely contribute to cardiac preload if used as a substitute for actual blood losses. This is not a pathophysiological surprise: Even the properly working vascular barrier is not able to retain electrolytes sufficiently. Therefore, the observed shift of 80% of an infused crystalloid is the inevitable consequence of a chosen therapeutical concept. Colloids, by contrast, are large molecules and therefore, they are retained. In this context strategies to protect the endothelial surface layer increasingly moved towards the centre of attention. This fragile structure is the main carrier of vascular barrier competence. It is severely altered by several noxas frequently present in the OR and in the ICU, including inflammation and ischemia/reperfusion injury, but also intravascular hypervolemia. Therefore, the latter iatrogenic pathophysiological condition should obviously be avoided as far as possible. The key to this might be a careful differential indication of isotonic crystalloids (maintenance) and iso-oncotic colloids (stabilising cardiac preload). For the surgical patient there is no sign in literature that this rational approach might not be safe. Beyond that, recent outcome data appeared to indicate a problem with hydroxyethyl starch in septic patients. A second careful view, however, reveals severe methodological shortcomings. Until today it is unquestioned that also septic patients in shock clearly benefit from immediate macrohemodynamical stabilisation. This might be achieved best by using colloids. After this very initial resuscitation phase the recent studies warn us to use hydroxyethyl starch in stabilized patients for several days in high cumulative doses. Accordingly, the remaining not very new message is not to use any drug outside a proper and careful indication.

Is it relevant to use balanced solutions?

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The clinical management of patients with hypovolemia, septic shock or hypovolemic/hemorragic shock; or those undergoing major surgery is based on several aspects, between them a fundamental role is played by the fluids therapy. Physician involved in management of critical patients have the responsibility of avoiding organ hypoperfusion, the latter being the first mechanism that tend to keep elevated plasmatic level of pro-inflammatory mediators [2] with the final result of maintaining patients hypovolemic. We know that we should give the right amount of fluids in the correct time [2]; we know that there is an inverse correlation between mortality and the quantity of fluids administered: the higher the amount the higher the mortality. Hence the correct strategy of fluids administration is to give enough fluids when they are really needed with the aim of avoiding an increased administration due to tissue hypoperfusion during the postoperative period.

However, it is not only a question of quantity fluids administered. Quality should play an equivalent fundamental important role. Indeed physician can choose between different strategies of fluids replacement therapy. First of all, they should decide on the use of either crystalloids alone or in combination with colloids. Then different type of both crystalloids and colloids should be considered. Presently, different crystalloids are available, such as Normal Saline (NS), Lactate Ringer solution, Balanced solution, Glucose solution. The same is true for colloids: Albumin, Gelatine and Hydroxyethyl starches are frequently used in the clinical setting, although their pharmacokinetic properties are very different. Finally, colloids can be diluted in either normal saline or balanced solution.

The consequence of the availability of these different solutions is that clinicians should be aware of their physical and chemical characteristics so that ideally the right solution should be given to the right patient. Physicians should know the composition of the solutions used in the clinical setting. One of the most used crystalloid all around the word is the NS, which is prepared with 154 mEq of both Na+ and Cl-. Since the plasmatic concentration of both electrolytes is markedly different from that present in the NS (especially for Cl-), it is axiomatic that administration of NS will alter the plasmatic electrolytes concentration. Indeed Na+ and Cl- will rise while Calcium and Magnesium should decrease because of the hemodilution effect due to fluids administration. Moreover, it is well known that a fluid strategy based on NS will alter the pH of the patient, by creating an hypercloremic acidosis, which is increasingly recognized as a clinical entity that had gone otherwise unnoticed for decades. The clinical relevance of this acid-base disorder is under debate mostly because there is a trend in current evidence to suggest that hyperchloremic acidosis may have important adverse consequences which may be circumvented by the use of balanced solutions. These consequences, both theoretical and clinical, may result from hyperchloremia, acidosis, or both.

To verify the clinical relevance of the NS administration on pH, electrolytes plasmatic concentration, renal function and inflammatory response to surgery, we randomised two groups of patients undergoing major abdominal surgery to receive either NS and HES 130/0.42 diluted in NS (group NS); or balanced solution and HES 130/0.42 diluted in balanced solution (group B). This was a double blind prospective, randomised trial. The group treated with balanced solution both in terms of crystalloids and colloids had a different behaviour compared to the group treated with normal saline, both in terms of colloids and crystalloids. As expected, the use of NS was associated with a lower pH, a lower base excess and higher chloride plasmatic concentration. In other words, patients treated with NS exhibited hypercloremic acidosis which is responsible of a various clinical effects, such as:

1. influence on coagulation. In aortic aneurysm surgery, it was shown that there was an increased blood product requirement in the saline group [4]. This has been observed in several studies. [4, 5, 6]. Thromboelastography indicates more effects on coagulation and platelet function with saline

when compared with a balanced salt solution. This is confirmed also during hemorrhagic shock [7];

2. renal vasoconstriction, increased renal vascular resistance (approx. 35%), decreased GFR (approx. 20%), reduction in diuresis, suppression of renin activity and reduction in blood pressure [8, 9, 10]. In our patients, the use of balanced solutions, both in terms of colloids and crystalloids, resulted in a statistically less increase of NGAL, which is a very sensitive marker of tubular cellular damage.

However, the two groups differed also for other plasmatic electrolytes. Surprisingly, a fluid resuscitation therapy based on NS was associated with lower plasmatic concentration of Calcium and Magnesium. This is of clinical interest because both electrolytes are relevant for patient's safety. Calcium is relevant for excitation-contraction coupling (cardiac arrhythmias), ciliary movements, hormonal secretion and coagulation, whilst clinical manifestation of Mg2+ deficit includes tetany, seizures, cardiac arrhythmias, neuromuscolar irritability, hypocalcemia and hypokalemia.

As previously pointed out (see above) surgery or sepsis or septic shock are associated with large production of cytokines and fluids therapy is particularly relevant in these patients. Hence the effects on inflammation are particularly interesting since different solutions can have different effects on inflammatory mediators. Colloids solutions can influence the activity of pro- inflammatory cascade [11]. This is of clinical interest. The ability to modulate the pro-inflammatory cascade can ameliorate organ function, as it has been demonstrated for acute lung injury and after surgery [12]. Our study demonstrates that, although there was no differences between the two groups in terms of the production of IL-6 and IL-8 (pro-inflammatory cytokines), the group treated with balanced solution had at the end of surgery a statistically significant increased plasmatic level of IL-10, which is the most powerful anti-inflammatory cytokine. In other words, administration of balanced solution was associated a faster recovery, at least from the inflammatory point of view.

In conclusion

1. *Different solutions are available in the clinical setting. They have different pharmacokinetic and pharmacodynamic properties and hence different effects. Both crystalloids and colloids must be seen as a drug. The effects depend on the solutes used (composition) and on their concentration in the blood and the quantity administered (as it is for every drug!).*
2. *The ideal solution should be similar to plasma as much as possible. Balanced solutions have been developed to reach this goal.*
3. *The use of Normal Saline is associated with hyper-chloremic acidosis, hypo-calcemia and hypo-magnesemia*
4. *There is a tight relationship between inflammation and volume replacement.*
5. *Both colloids (HES) and crystalloids can modulate inflammation by acting directly on one of the "products" of the inflammatory cascade.*

Is it relevant to use balanced solutions?

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Fluid Management in Pediatrics

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Background Maintenance fluid therapy in children has been based for half a century on Holiday and Segar's recommendations suggesting the use of hypotonic fluids with 5% glucose added. As a consequence of surgical trauma, emergencies or critical illness children may have a stress-induced secretion of antidiuretic hormone (ADH) leading to an impaired ability to excrete free water. In recent years many studies and case reports have shown that the routine use of hypotonic fluids with 5% glucose may lead to serious hyponatremia or hyperglycemia, and this can easily be avoided by the use of isotonic instead of hypotonic solutions.

Crystalloids The composition of extracellular fluid volume (ECFV) is comparable in both children and adults. Therefore similar electrolyte solutions can be used for maintenance or restoring ECFV independent of age. As in adults the balanced electrolyte solutions (BEL) reflect the physiological electrolyte concentrations of the ECFV of the children and acetate as bicarbonate precursor can be used even in neonates and preterms. As a consequence the modern BEL have a higher intrinsic safety and a lower incidence of side effects (hyponatremia, hyperchloremic acidosis, fluid shifts, lactate accumulation) when compared to hypotonic solutions, normal saline or Ringer's lactate in both the adult and pediatric age groups.

Colloids Children have less colloid osmotic pressure (COP) and a higher interstitial fluid volume. Therefore the intravascular volume effect of crystalloids is lower in neonates and infants when compared to older children and adults. Traditionally albumine solutions were used frequently in children for volume replacement but recently numerous studies showed that modern hydroxyethyl starch solutions (HES) or modified fluid gelatin (GEL) are as safe and effective but less expensive when compared to natural colloids even in neonates and small infants.

Glucose Children have also a higher risk of lipolysis and hypoglycemia caused by a higher metabolic rate than adults. The administration of glucose free solutions may increase the risk of lipolysis with the release of ketone bodies and free fatty acids. Therefore, intraoperatively the use of isotonic fluids with lower glucose concentrations (i.e. 1 to 2.5%) is a well accepted compromise between avoiding hypoglycemia/lipolysis and hyperglycemia in children.
Postoperatively the glucose concentrations should be increased to 2.5 to 5%.

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Fluid management in cardiac surgery

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The typical scenario of cardiac surgery is a mix of stressful conditions all around the cardiopulmonary bypass (CPB), the distinctive feature of this surgery. Heterogeneous flows, hemodilution, hypoperfusion and ischemia-reperfusion injuries, hypothermia, coagulation disorders, are all constant topics of the cardiac patients scheduled for intervention. Fluids can play an important role in many of these issues. The continuous change of fluid balance along the perioperative period is particularly challenging for the cardiac anesthesiologist. Moreover cardiac surgery shows worldwide the highest in-hospital transfusion rate of blood and blood products (>70%).

Hypovolemia, absolute or relative, is very frequent in cardiac surgery, itself able to amplify the inflammatory reaction through a waterfall of events in capillary beds. Vicious circles maintain a dangerous condition for organ perfusion, sometimes exiting in organ dysfunction and worse outcome for our patients. CPB is especially associated with changes of intra and extravascular volume status, often resulting in cardiopulmonary dysfunction. It is common experience that a priming composed mainly of colloids induces higher colloid-osmotic pressure and consequent protection against pulmonary fluid extravasation. Moreover a priming made by colloids causes a volume effect persisting longer in the postoperative phase, mandating less volume expansion with artificial colloid during the first 24 postoperative hours and not causing additional allogeneic blood component exposure.

Patients undergoing cardiac surgery with extracorporeal circulation are at high risk for electrolyte depletion, despite supplementation of some electrolytes, such as potassium and magnesium. The probable mechanism is a combination of increased urinary excretion and intracellular shift induced by a combination of extracorporeal circulation and decreased body temperature during surgery (hypothermia-induced diuresis). There are several conditions associated with hypomagnesemia, and there is a high incidence of hypomagnesemia in patients admitted to an intensive care unit (ICU), almost 61% in postoperative. Patients undergoing coronary artery bypass surgery are more likely to show magnesium deficiency than non-cardiac surgical patients. A more recent review confirmed the efficacy of intravenous magnesium in preventing postoperative atrial fibrillation compared with placebo or control (beta-blocker sotalol).

Our experience on more than 700 cardiac surgical patients showed that a CPB prime made by tetrastarches reduced perioperative fluid balances, allogeneic blood transfusions and postoperative need of sternal reopening for bleeding. Moreover renal function was not affected, even in a high-risk subgroup of patients subjected to coronary angiography <48hours before surgery. Comparing priming volumes with balanced or unbalanced tetrastarches, the group of patients treated with balanced solutions showed less incidence of postoperative hypomagnesemia and atrial fibrillation, which translated in less ICU length of stay.

Fluid management in cardiac surgery

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Fluid Management in septic patients

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In severe sepsis and septic shock, adequate fluid replacement is one of the essential therapeutic requirements to restore and maintain circulating plasma volume in order to improve organ perfusion and nutritive microcirculatory flow [1]. It has been shown that early goal-directed fluid resuscitation in patients with severe sepsis and septic shock is associated with improved outcome [2]. The question of which type of solution should be used as a fluid replacement controversial [3]. However, Trof et al. showed very elegantly, that the use of a colloid results in early sepsis in increased preload and increased oxygen delivery [4]. Thus, a colloid stays in this critical phase of sepsis treatment in the intravascular space, increasing thereby plasma volume and is not leaking out.

In Europe, mostly artificial colloid solutions are used on the basis of gelatin and hydroxyethyl starches (HES). In critical ill patients, acute renal dysfunction frequently deteriorates to renal failure due to hypovolemia, hypoxia, hypoperfusion and toxity of drugs (for example, anti-infectives), as well as endothelial damage inducing pro-inflammatory response finally resulting in organ dysfunction. Thus, the evaluation of colloid associated effects in this context is difficult. Sepsis is also often associated with impaired renal function. The effect of HES infusion on renal function in sepsis patients has spurred ongoing research on the underlying pathology. Experimental data could demonstrate evidence that the effect of HES on renal function depend on the HES formulation used. Thus, in experimental setting 6% hydroxyethyl starch 130/0.42 significantly preserved renal function and attenuate tubular damage better than 10% hydroxyethyl starch 200/0.5 [5]. However, in a recent clinical randomized control trial (not published yet), 6% hydroxyethyl starch 130/0.42 was associated with increased mortality compared to ringer's acetate. On the other hand, when compared to starches, gelatin solutions are associated with a lower risk of acute renal failure (odds ratio 0.43, 95% confidence interval 0.20 to 0.92; P=0.03) [6].

In summary, the use of a colloid in the treatment of septic shock is effective. HES cannot be recommended in septic patients according to the existing evidence. The use intravenous gelatin as a plasma expander is safe and recommended in septic patients. However, in view of the current available evidence more prospective clinical data would further the benefit associated with the use of gelatin solutions.

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Balanced volume therapy in transplant patients

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Background

Proper fluid management is essential for maintaining circulatory function an adequate perfusion. Intravascular volume replacement is important to outcomes in surgical patients, particularly transplant patients whose blood loss may be high intra-operatively. There is much debate over the appropriate fluid for intravascular volume expansion ranging from crystalloids to colloids. Crystalloids have been shown to be equally effective for colloids in some patient populations (1). However. colloids remain frequently used in critically ill and surgical patients. The belief is that colloids increase the proportion of fluid that remains intravascular thus improving the efficiency of volume repletion.

Among the colloids, the synthetic hydroxyethyl starch (HES) has become popular as an alternative to the naturally occurring colloid, albumin. HES is less expensive than albumin and as a synthetic carries no infection risk (2).

HES solutions comprise of polygluscose chains of various molecular sizes and the vehicle used to dissolve the colloid is 0.9% NaCL. While HES is widespread in use, the safety and efficacy of this colloid compared to albumin has not adequately determined by current published studies (3). Studies have suggested a possible increase in bleeding among cardiopulmonary bypass patients as well as an increase in renal failure with HES use (4, 5). Other studies refute these findings, finding equivalent outcomes on renal outcome between liver transplant patients given albumin versus 130/0.4 HES (2, 10, 11).

It has been suggested that balanced hydroxyethyl starch solutions may lessen the potential adverse effects of this colloid, although this finding has not been consistent among published studies (6). The balanced solutions replace inorganic chloride with an organic class 2 anion (i.e. lactate or acetate). These organic anions are converted to bicarbonate by hepatic and renal metabolism (7). Such a solution, HES-bal (Tetraspan®, B. Braun, Melsungen, Germany) has several advantages: preserved hemodynamic effect; retention in circulation not exceeding the duration of the hemodynamic effect; preserved acid base homeostasis (8).

This study aims to analyze the short-term outcomes of the use of HES-bal (Tetraspan) in patients undergoing heart and liver transplant. During the 2 week perioperative period blood clotting, renal function, mechanical ventilation duration, acid base balance and mortality have been analyzed in transplant patients receiving HES-bal. The cohort of analyzed patients is too small to be conclusive in comparing Tetraspan® with other crystalloids or colloids and further studies will be necessary.

Methods

Patients receiving heart of liver transplant within the past 6 months at ISMETT were retrospectively analyzed. Crystalloid and colloid type and amount were recorded intra operatively, 48 hours post operatively and at 7 days post operatively. Impairment of bleeding was assessed through recording INR post operatively as well as haemoglobin level and units of pRBC and/or FFP transfused. Renal function was analyzed by changes in serum creatinine after receiving fluids from baseline. Adverse events, including anaphylaxis or morbidity or mortality were also collected. We recorded moreover the number of days on mechanical ventilation.

In conclusion

Irrespectively of transplanted solid organ, no abnormalities in all the examined settings were registered as due to administration of Tetraspan, the infusion of which seems to be safe and effective in the clinical scenario of solid organ transplantation.

Balanced volume therapy in transplant patients

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Fluid Management in Trauma

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The question as to the optimal volume replacement for compensating intravascular blood loss is subject of ongoing controversy. Ever since the results of the Cochraine Injuries Group Albumin Reviewers were published, the use of albumin has markedly declined (1). Dextrans are also hardly used anymore for volume therapy. Their extremely negative effects on the coagulation system mean they could be used as anticoagulants, if at all, and not for volume therapy (2).

1. Crystalloids or colloids?

Whether colloid infusions are generally superior to crystalloids has also not been conclusively answered. A meta-analysis by Schierhout and Roberts analyzed 26 studies with 1,622 patients. The authors came to the conclusion that the administration of colloids is associated with enhanced mortality (3). A different meta-analysis by Choi et al. reviewed 17 studies with 814 patients. Only the subgroup of multiple traumatized patients showed a lower rate of mortality for crystalloids as compared to colloids (4). Whether these meta-analysis are conclusive for European and Asian conditions is questionable. The studies involved were primarily US American studies and thus employed dextrans and hetastarches (high molecular hydroxyethyl starch preparations with a high substitution degree), which have not been used for a long time in Central Europe and most Asian countries because of their high potential for side-effects, particularly involving the coagulation system.

Crystalloids are not very effective to restore intravascular blood loss because they disappear into the interstitium and cause edema. On the other side, crystalloids impair the coagulation system primarily only by means of their dilutional effect in contrast to colloids. Several studies surprisingly postulated that low doses of crystalloids as well as colloids cause hypercoagulability. These were primarily in vitro studies using non-activated TEG (thrombelastography) measurements. Despite the shortened clot formation times and enhanced clot strengths seen for TEG, no change in the activated coagulation markers (thrombin-antithrombin complex) was observed (5-9). It is possible that the measured shortened clot formation times and enhanced clot strengths are the result of an in vitro effect produced by the influence of the sedimentation of red blood cells in diluted specimens subject to long measuring time (10). Measuring with activated TEG and markedly shortened measuring time was, however, not able to confirm this phenomenon (11, 12). Moreover, Petroianu et al. concluded that hemodilution with crystalloids and colloids caused a decrease in the activity of various clotting factors in vitro (13). Thus, why hemodilution should activate coagulation while activated coagulation markers remain unchanged and the activity of various factors and the platelet count decrease, is not known.

Gelatin solutions are available in most European and Asian countries. From clinical aspects, they have nearly the same volume effect compared to starches.

Compartment	Glucose 5%	Crystalloid	Colloid
intravascular	↑	↑	↑↑↑
interstitial	↑↑	↑↑	
intracellular	↑↑↑		

Further benefits compared to starches are:

2. No accumulation in the reticuloendothelial system (RES) or other tissues.
2. No effect on kidney function.
3. Less effects on coagulation/fibrin polymerization.
4. No dose limitation.

In addition to their dilutional effect gelatin preparations also exert specific effects on the coagulation system. Above all they impair fibrin polymerization and disturb the network of the fibrin monomers (14-15).

Hydroxyethyl starch (HES) has been reported to be associated with an increased tendency to bleed, kidney injury as well as accumulation in the RES with unknown effects on the immune system above all when using solutions with a high molecular weight and a high replacement degree (16). HES solutions cause a von Willebrand type 1-like syndrome characterized by diminished FVIII activity and diminished vWF plasma levels (17). In addition, HES also impairs fibrin polymerization. A relatively new preparation is 6% HES 130/0.4 (Voluven®, Fresenius, Pharma Austria GmbH); it has a medium molecular weight and a low substitution degree and thus probably does not as strongly affect the coagulation system as old fashioned starch solutions (18, 19). Nevertheless, also so called "modern" median weight starches seem to disturb fibrin polymerization significantly more compared to gelatin.

2. Balance or unbalanced fluid resuscitation concepts?

Avoidance of acidosis by the choice of volume replacement regimen is of major clinical importance because acidosis/increased base excess is an important marker for tissue and organ hypoperfusion as well as hypovolemia. Large amounts of unbalanced/saline based fluids cause hyperchloremic acidosis. It should be taken into account that base excess is a predictor for outcome in critical care patients.

The clinical relevance of hyperchloremic acidosis is not completely elucidated. Some authors emphasize that infusion related hyperchloremic acidosis is benign while others stress the importance of a well adjusted metabolic system. Nevertheless, the British Consensus Guideline on intravenous fluid therapy for adult surgical patients favors the use of balanced solutions compared to the use of saline for volume replacement (20). In a study in elderly patients undergoing mayor surgery, a combination of balanced crystalloids and colloids resulted in a prevention of metabolic acidosis and in an improved gastric mucosal perfusion compared to patients who received saline as well as starch solution dissolved in saline (21).

In conclusion

In summary, crystalloids are not very effective in volume replacement following major blood loss or severe intravascular volume depletion. Administration of huge amounts of crystalloids causes edema which may disturb microcirculation.

In critically ill patients as well as in patients with severe hemorrhagic shock and need for intravascular volume replacement we prefer gelatin solutions at our institution because of less side effects on the coagulation system/fibrinogen polymerization, less accumulation in the RES, less effects on kidney function and because of the missing dose limitation compared to starch solutions. Even if there is no evidence that administration of balanced solutions improves outcome parameters like morbidity and mortality in clinical trials (clinical endpoints like morbidity/mortality), administration of balanced solutions avoids the occurrence of acidosis as opposed to saline.

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