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## Intraoperative fluid therapy-crystalloid/colloid debate

Joachim Boldt, M.D., Ph.D\*

\* Department of Anesthesiology and Intensive Care Medicine, Klinikum der Stadt Ludwigshafen, Germany.

### INTRODUCTION

Absolute or relative blood volume deficits often occur in the perioperative period. Bleeding may cause absolute volume deficits - vasodilation mediated by vasodilating substances (e.g. anaesthetics) or rewarming is involved in producing relative volume deficits. Fluid deficits can also develop in the absence of obvious fluid loss secondary to generalized impairment of the endothelial barrier resulting in diffuse 'capillary leak' (e.g. during inflammation).

The increasing awareness of the risk of transmitting viral diseases results in more aggressive use of nonsanguinous volume replacement. As shown by various studies reduction in hematocrit and in arterial oxygen content is not deleterious even in "high risk patients" since compensating mechanisms are able to guarantee tissue oxygenation and systemic oxygen transport. Careful attention is necessary to evaluate the patient's oxygen carrying capacity. Although extensive information is available on the use of hemodilution, the 'safe' hemoglobin level is still not definitely known. In the elderly and the critically ill surgical patient it has to be taken into account that limitations of cardiac and pulmonary function will influence the components of oxygen delivery. Nevertheless, blood/blood component therapy should be restricted to those cases presenting severe anaemia or coagulation disorders. Non-blood alternatives for volume replacement in these patients have to be defined. The choice between colloid and crystalloid solutions continues to generate controversy<sup>(1-6)</sup>. The highly controversial crystalloid/colloid debate has been enlarged to a colloid/colloid debate because aside from the natural colloid albumin several other colloids are available as plasma substitutes<sup>(7)</sup>. The 'historical' crystalloid/colloid controversy has been focused primarily on outcome. New concepts about critical care, the role of inflammation,

immunological aspects, and wound healing may change this point of view.

Five major aspects are of importance when volume replacement is considered:

1. the type of fluid must be decided,
2. the amount of fluid must be defined,
3. the criteria for guiding volume therapy must be defined,
4. possible side effects should be considered,
5. costs are of importance.

### PRINCIPLES OF VOLUME REPLACEMENT

Hypovolemia is associated with flow alterations that are inadequate to fulfill the nutritive role of the circulation. During hypovolemia-related hemodynamic dysfunction the organism tries to compensate perfusion deficits by redistribution of flow to vital organs (e.g. heart and brain) resulting in an underperfusion of other organs such as gut, kidneys, muscles, and skin. Activation of the sympathetic nervous system and the renin- aldosterone-angiotensin system (RAAS) are compensatory mechanisms to maintain peripheral perfusion. Various circulating vasoactive substances and inflammatory mediators are additionally released in this situation. Although this compensatory neurohumoral activation is beneficial at first, this mechanism becomes deleterious and may be involved in bad outcome of the hypovolemic critically ill patient. Thus adequate restoration of intravascular volume remains an important therapeutic maneuver in managing the surgical patient. The administered fluid may stay in the intravascular compartment or equilibrate with the interstitial/intracellular fluid compartments. The primary goal of volume administration is to guarantee stable hemodynamics by rapidly restoring circulating plasma volume. However, excessive fluid accumulation, particularly in the interstitial tissue

should be avoided. Hypothesis of Starling describes and analyses the exchange of fluid across biological membranes. In this equation colloid oncotic pressure (COP) is an important factor in determining fluid flux across the capillary membrane between the intravascular and interstitial space. Thus manipulation of COP appears to be promising for guaranteeing adequate circulating intravascular volume.

The magnitude and duration of this volume effect will depend on

1. the specific water binding capacity of the substance,
2. how much infused substance stay in the intravascular space.

Because of the varying physico-chemical properties the commonly used solutions for volume replacement differ widely with regard to COP, initial volume effects, and duration of intravascular persistence.

## POSSIBLE STRATEGIES FOR PERIOPERATIVE VOLUME REPLACEMENT

### Crystalloids

Crystalloids can be divided into hypotonic (e.g. dextrose in water), isotonic (e.g. lactated Ringer's solution) and hypertonic solutions (e.g. 7.5% saline solution). When selecting the solution for volume replacement the electrolyte status of the patient must be kept in mind. Crystalloids are freely permeable across the vascular membrane and are therefore distributed in the plasma and interstitial/intercellular fluid compartments (Table I). Crystalloids are mainly distributed to the interstitial space (ISS), colloids mainly to the intravascular space (IVS). After infusion of 1,000 ml of saline solution, plasma volume was expanded by only 180 ml<sup>(8)</sup>. Consequently large quantities of fluid (at least 4 to 6 times the actual intravascular volume deficit) have to be infused to achieve normovolemia when crystalloid fluid regimen is chosen. Moreover, due its very limited volume stabilizing effects, crystalloid infusions have to be repeated to maintain filling. When infusing such high quantities of unbuffered saline, hyperchloremic acidosis could complicate this type of fluid therapy. Moreover, severe dilution of plasma protein concen-

tration is accompanied by a (critical) reduction in plasma COP with the risk of increasing interstitial edema. Thus volume replacement regimen based only on infusion of high amounts of crystalloids which are necessary to guarantee hemodynamic stability seems to be less qualified<sup>(9,10)</sup>. Stein et al<sup>(11)</sup> demonstrated that 70% of the elderly patients suffering from circulatory shock and having received crystalloids for volume stabilization developed pulmonary edema in contrast to 25% of the colloid-treated group. A massive crystalloid resuscitation alone is less likely to achieve adequate restoration of blood flow and tissue O<sub>2</sub><sup>(12)</sup>. In an animal (hemorrhage) experiment Wang et al<sup>(13)</sup> investigated the quality of fluid resuscitation by laser Doppler flowmetry (LDF). They concluded from their results that lactated Ringer's solution did not restore microvascular perfusion sufficiently in this situation. Others also have shown that colloids are able to restore (microcirculatory) perfusion more than crystalloids<sup>(14)</sup>. In a model of sepsis using animal experiments greater capillary luminal area, with less endothelial swelling and less parenchymal injury was found with colloid infusion (hydroxyethyl starch [pentastarch]) than with Ringer's lactate<sup>(15)</sup>.

### Colloids

*The available colloids differ in their pharmacological characteristics and subsequently in their clinical effects.*

#### Albumin

Albumin is a naturally occurring plasma protein and has for long been judged to be the kind of solution by which the patients would profit most ("gold-standard"). Although albumin is derived from pooled human plasma there should be no risk of disease transmission because albumin is heated and sterilized by ultrafiltration. In terms of transmission of infectious diseases, albumin is generally considered to be safe. The molecular weight of albumin is 69,000 dalton. 4% albumin is hypo-oncotic, 5% albumin is iso-oncotic, whereas 20% and 25% solutions are hyperoncotic. In "old" studies the oncotic force of concentrated human albumin (e.g. 20%) have been shown to reduce pulmonary edema. These effects of albumin depend on its movement between the intravascular and extravascular compartments and greatly varies with regard to the patient's disease. In patients with altered vascular endothelial integrity (e.g. after cardiac surgery), albumin may pass into the interstitial space, by which fluid shift from the intravascular compartment may be promoted, interstitial volume is substantially increased<sup>(16)</sup>, and tissue perfusion may be altered. Several recently published studies have questioned the value of using albumin for volume replacement in the critically ill. People have been born without albumin (congenital analbuminemia) and several patients are remarkable asymp-

**Table I.** Optimal solution for volume replacement in the surgical patient.

- |   |
|---|
| — free of risk of transmitting diseases           |
| — intravascular stay                              |
| — promote minimal interstitial water accumulation |
| — improve (microcirculatory) organ perfusion      |
| — induce no coagulation disorders                 |
| — free of other detrimental side effects          |
| — inexpensive                                     |

tomatic<sup>(17)</sup>. Thus what is the role of albumin: vital component or place-holder, hero or poseur?

#### “Synthetic“ colloids

The term “synthetic” colloids is somewhat misleading because all are of biological origin - albumin is also “synthesized” (from pooled plasma). Thus the term “non-protein” colloids appears to be more precisely. In contrast to the natural colloid albumin, which is a monomer (i.e. all molecules have the same size and weight), synthetic colloids are polydispersed, i.e. they are a combination of many differently sized molecules. Large molecules only contribute minimally to the volume expansion effects, they reflect viscosity and persistence in the circulation. Smaller molecules of this solutions are quickly lost by renal filtration or diffusion into the interstitial space.

#### Dextrans

Dextrans are a polydispersed mixture of glucose polymers. 6% dextran 70 (average molecular weight 70,000 dalton) and 10% dextran 40 (average molecular weight 40,000 dalton) are the two available dextran preparations. Increase of plasma volume after infusion of 1,000 ml of dextran 70 ranged from 600 to 800 ml. The main differences between the two solutions concern their influence on microcirculation. Infusion of dextran 40 has been described to increase microcirculatory flow because of a reduced red cell and platelet sludging, volume expansion, and haemodilution-induced reduction in whole blood viscosity. Dextrans, however are associated with severe side-effects (e.g. anaphylactic reactions, coagulation abnormalities) and impaired blood cross-matching so that they have been replaced by other synthetic colloids in several countries.

#### Gelatins

Gelatins are modified beef collagens. Gelatin was introduced in 1915 for shock treatment and was used rather extensively during World War I. Gelatin is listed by the World Health Organization as an essential drug. In the USA, however, gelatin was abandoned in 1978 due to its high incidence of hypersensitivity reactions. Gelatin exists in three different modifications: cross-linked gelatin (e.g. Gelofundiol®), urea-linked gelatin (e.g. Haemaccel®), and succinylated gelatin (e.g. Gelofusine®). The only major differences between these preparations consist in different electrolyte concentrations: urea-linked gelatin includes high calcium and potassium contents, succinylated preparations have low calcium and potassium contents. The increase of blood volume is approximately the same as that of the infused volume of gelatin. Due to the

low molecular weight average (approximately 35,000 dalton) plasma half-life is only short (maximal two hours) so that re-infusions of gelatins are necessary to maintain blood volume sufficiently.

#### Hydroxyethylstarch (HES) preparations

HES preparations widely differ with regard to their physicochemical properties. HES is a derivative of amylopectin, which is a highly branched compound of starch. In humans and animals amylopectin is rapidly hydrolysed by alpha-amylase and renally excreted. In order to slow down the metabolic degradation, anhydroglucose residues of the amylopectin are substituted with hydroxyethyl groups. The hydroxyethyl groups can be introduced mainly at positions C2 and C6 of the anhydroglucose residues. HES preparations are characterized by

1. concentration (3%, 6%, 10%),
2. weight average molecular weight (Mw: the sum of each molecule's weight divided by the total mixture's weight times the weight of the molecule)
  - low-molecular weight [LMW]-HES: 70,000 dalton;
  - medium-molecular weight [MMW]-HES: 130,000 to 260,000 dalton;
  - high-molecular weight [HMW]-HES: > 450,000 dalton,
3. molar substitution (MS: the molar ratio of the total number of hydroxyethyl groups to the total number of glucose units,
  - low MS: 0.4 and 0.5;
  - moderate MS: 0.62;
  - high MS: 0.7
4. and the C2/C6 ratio. The ratio of the C2:C6 hydroxyethylation appears to be key factors for pharmacokinetic behaviour of HES and possibly also for its side effects (e.g. accumulation).

In the USA only hetastarch (concentration: 6%; Mw: 450,000 dalton; MS: 0.7) is available at present for volume replacement. Pentastarch® (concentration: 10%; Mw: 260,000 dalton; MS: 0.45) is FDA approved only for plasmapheresis. Pentafraction, a diafiltered solution of hydrolyzed amylopectin similar to pentastarch, possess a narrower molecular weight range (Mw: 280,000 dalton; MS: 0.5) is not commercially available at this time. In Europe, the range of available HES solution is much wider and different combinations with regard to concentration, Mw, and MS are available. The extent and duration of plasma expansion are extremely dependent on the physical and chemical characteristics of the HES solution. Thus maintenance of hemodynamic stability seems to be highly dependent on the kind of HES-preparation used. The different HES prepa-

rations cause different effects on rheology, coagulation, oncotic pressure, and intravascular half-lives.

## SIDE-EFFECTS OF THE DIFFERENT VOLUME REPLACEMENT STRATEGIES

Theoretical and documented hazards are associated with each kind of volume therapy. One major concern towards the use of synthetic colloids particularly include possible alterations in the coagulation system<sup>(35)</sup>.

### Coagulation

Imbalances in the normal haemostatic mechanisms can commonly be seen in the surgical patient either due to marked blood loss, hypothermia, or activation of inflammatory pathways with subsequent activation of procoagulatory mechanisms and down-regulation of anticoagulant pathways. All plasma substitutes lower the concentration of clotting proteins by means of haemodilution. **Crystalloids** appear to have no major deleterious effects on coagulation although *in vivo* and *in vitro* experiments it has been shown that hemodilution *per se* (also with crystalloids) compromised blood coagulation<sup>(18,19)</sup>. The natural colloid **albumin** is widely considered to have no significant negative effects on blood clotting. It is generally accepted that **dextrans** negatively influence hemostasis either by reducing von Willebrand factor or by impairing platelet function<sup>(20)</sup>. This is one of the reasons why use of dextrans has been reduced markedly in most countries. When administering dextran, both VIIIIR:Ag and VIIIIR:RCo levels decrease significantly. Reduced VIIIIR-RCo is associated with reduced binding to platelet membrane receptor proteins GPIb and GPIIb/IIIa, which results in decreased platelet adhesion. Little is known of the effects of **gelatins** on perioperative hemostasis and they have been considered to be without significant influence on hemostatic competence. In an *in vitro* study, however, significant inhibition of platelet aggregation was demonstrated by two gelatin preparations (polygeline, and succinylated gelatin)<sup>(21)</sup>. In an *in vitro* study using 3.5% polygeline and 4% succinylated gelatin it has been shown that both gelatin preparations produced significant reduction in clot quality<sup>(22)</sup>. In a study in 6 healthy men infusion of 1L of gelatin resulted in a 1.7 fold increase in bleeding time, a substantial decrease in vWg:ag (-32%) and ristocetin co-factor (-29%), and a significant impairment of ristocetin-induced platelet aggregation<sup>(23)</sup>. Several studies on impaired haemostasis with subsequently increased bleeding tendency have been published with the use of **hydroxyethyl starch**. The majority of these studies used the old HMW-HES (Mw: 450,000 dalton, MS of 0.7 [Hetastarch]). This HES preparation may induce a type I von Willebrand-like syndrome with decreased factor VIII coagulant activity, and decreased von Willebrand's factor antigen and factor VIII-related

ristocetin cofactor. HMW-HES diminished the concentrations of VIIIIR:Ag and VIIIIR:RCo more pronouncedly than HES with lower molecular weight (LMW-HES). HMW-HES resulted also in the overall most pronounced impaired platelet aggregation<sup>(24)</sup>. Modern HES preparations (especially 3<sup>rd</sup> HES [HES 130/0.4]) did not show the same negative effects on platelet function as seen after HMW-HES administration<sup>(24)</sup>. Low and medium weight HES preparations (Mw 70,000 to 260,000 dalton) with a lower MS (0.4; 0.5) do not have such negative effects on coagulation outside of hemodilution<sup>(25-28)</sup>. In human several studies confirmed that these modern HES preparations can be safely used in the surgical patient.

### Storing and accumulation

Storing and accumulation may be another problem with synthetic colloids. Gelatins and dextrans are naturally occurring substances and consequently they are fully metabolized in man. The modified starch molecule is the basis of HES solutions - all preparations are stored and may accumulate. HES undergoes a slow intravascular catabolism by alpha-amylase. The smaller molecules are rapidly eliminated by glomerular filtration. Depending on the kind of HES preparation, a varying degree of the administered HES leaves the vascular department and is taken up by the reticulo-endothelial system (mononuclear phagocytic system [MPS]). The sequelae of storage of HES are not well clarified. With regard to the MPS storage of HES molecules appears to be without detrimental consequences<sup>(29)</sup>.

### Anaphylactic/anaphylactoid reactions

All colloids used for volume therapy including the natural colloid albumin have the potency to induce anaphylactic/anaphylactoid reactions<sup>(30)</sup>. Most commonly known in severity and frequency are dextran-induced anaphylactic reaction and even prophylaxis with monovalent hapten dextran cannot completely eliminate their occurrence<sup>(31)</sup>. In a large clinical trial including approximately 20,000 patients it was demonstrated that some gelatins produce a larger number of anaphylactic/anaphylactoid reactions than other plasma substitutes<sup>(32)</sup>. Modern (e.g. urea-linked) gelatin preparations seems to be associated with less incidence of inducing anaphylactic reaction compared with succinylated gelatin. Severe (life-threatening) anaphylactic reactions with the different kinds of HES preparations may also occur but appear to be rare<sup>(32)</sup>.

### Renal function

Impaired renal function is one of the problems with the use of colloids. The effects of the different volume replacement regimens on renal function are controversially discussed. Generally, **gelatins** appear to be without major damaging effects. In-

creased creatinine levels in patients treated with (1<sup>st</sup> generation) HMW-HES (450/0.7) have been shown. In a retrospective analysis of patients undergoing kidney transplantation and in whom HES with a high DS (0.62) was infused, “osmotic-nephrosis-like lesions” were seen<sup>(33)</sup>. These lesions, however, have no negative influence on graft function or serum creatinine 3 and 6 months after transplantation. Cittanova et al.<sup>(34)</sup> demonstrated that the use of 6% HES 200/0.62 (2,100 ± 660 ml) in brain-dead donors resulted in impaired renal function in kidney transplant recipients (higher serum creatinine concentrations and a more frequent incidence of hemodialysis compared to a gelatin-treated group). Thus, HES preparations with high molecular weight and/or high MS may have detrimental consequences for renal function. Modern HES preparations with different physico-chemical characteristics (lower Mw, lower MS [e.g. HES 130/0.4]) has been shown to have no more negative influence on kidney function. The most likely mechanism for inducing renal dysfunction is the induction of hyperviscosity by (repeated) infusion of hyperoncotic colloids in dehydrated patients. Glomerular filtration of hyperoncotic molecules from colloids causes a hyperviscose urine and a stasis of tubular flow resulting in obstruction of tubular lumen.

## OUTCOME AND VOLUME REPLACEMENT STRATEGIES

Reviewing the present literature, it has not been proven that by the choice of a certain plasma substitute someone's life can be saved. Even the recently published SAFE study<sup>(36)</sup> in intensive care patients did not show an advantage of one of the two used plasma substitutes (saline solution versus human albumin).

In cardiac surgery there is one major study showing an influence on patients' outcome (mortality): In a retrospective chart analysis in 19,578 patients undergoing CABG surgery, patients receiving albumin or nonprotein colloids (dextrans of hetastarch) were studied<sup>(55)</sup>. Mortality was lower in the albumin group compared to the nonprotein colloid group (2.47% vs 3.03%,  $p = 0.02$ ). The value of such retrospective studies has been often doubted. Unfortunately, the type of colloid has not been distinguished (one group: dextrans and starches) and the reason why colloid-treated patients showed a higher mortality has not been shown. Looking at the complications associated with this two colloids, it may be speculated that bleeding may be the major reason – a complications that easily could have been avoided by using a more modern non-protein colloid.

## CONCLUSION

A well-balanced volume therapy is essential in managing patients undergoing surgery. The ‘ideal’ plasma substitute for volume replacement remains a matter of dispute (Table I). Merits and demerits of colloids versus crystalloids for volume re-

placement have been discussed very emotionally. Recently published meta-analyses or evidence-based medicine analyses appear to be less helpful to solve this problem. With their conflicting results more questions arise than answers are given.

Perioperative fluid requirements will depend on the length and complexity of surgery. The primary goal for volume replacement therapy is to augment intravascular volume and to maintain stable haemodynamics. Pros and cons of each solution for volume replacement have to be considered. The choice of solution for maintenance of circulating volume in the individual patient should be based on the pharmacokinetics and pharmacodynamics of the used solution as well as on the pathophysiology of the patients' underlying disease. In spite of the absence of any definitive evidence of superiority, consensus guidelines have been published with regard to the use of the different solutions for volume replacement. Although crystalloids appear to be less likely appropriate for resuscitation of the intravascular space (IVS) because they are mainly distributed to the interstitial space (ISS), crystalloids have been recommended as the initial fluid of choice in patients resuscitating patients from haemorrhagic shock<sup>(37)</sup>. Are we any wiser concerning the crystalloid/colloid problem? Researchers who show crystalloids to be superior always find crystalloids superior and consider colloids as ‘luxury items’. Human albumin is still widely used for volume replacement in the absence of convincing supportive data in the literature. Effective alternative fluids are synthetic colloids. The different preparations appear to be without major differences with regard to their hemodynamic efficacy, but they show varying effects on microcirculation and organ perfusion and are associated with different unwanted negative effects (coagulation; anaphylactic reactions). The lower costs of these solutions is a powerful argument for using synthetic colloids rather than albumin.

There are no convincing guidelines regarding the choice of fluid for volume replacement in the surgical patient. The Holy Grail of volume replacement has not been found, it has to be doubted whether there will be a definite solution of this problem. Conflicting results from different studies are most likely due to variations in clinical protocols, selection of patients, criteria for blood or volume administration. A randomized control trial comparing two different solutions would require over 6,500 (comparable) patients to detect excess mortality of 4%<sup>(38)</sup>. Which fluid is more effective will hardly be answered adequately in terms of mortality. It has been questioned whether meta-analyses are helpful to examine the effects of crystalloid or colloid fluid resuscitation on mortality<sup>(39)</sup>, because mortality was never an end point of any of the crystalloid/colloid studies. It seems to be a fantasy to save someone's life by choosing a kind of fluid for volume replacement in the perioperative period. Effects of different fluids should be better focused on organ function, endothelial inflammation, perfusion, or other physiological variables.

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