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REVIEW ARTICLE

Perioperative Fluid Management and Clinical Outcomes in Adults

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The administration of IV fluid to avoid dehydration, maintain an effective circulating volume, and prevent inadequate tissue perfusion should be considered, along with the maintenance of sleep, pain relief, and muscular relaxation, a core element of the perioperative practice of anesthesia. Knowledge of the effects of different fluids has increased in recent years, and the choice of fluid type in a variety of clinical situations can now be rationally guided by an understanding of the physicochemical and biological properties of the various crystalloid and colloid solutions available. However, there are few useful clinical outcome data to guide this decision. Deciding how much fluid to give has historically been more controversial than choosing which fluid to use. A number of clinical studies support the notion that an approach based on administering fluids to achieve maximal left ventricular stroke volume (while avoiding excess fluid administration and consequent impairment of left ventricular performance) may improve outcomes. In this article, we review the available fluid types and strategies of fluid administration and discuss their relationship to clinical outcomes in adults.

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Available IV fluids vary in their biological and physicochemical properties. Choice of fluid in clinical practice should be guided by an understanding of these differences. Hemorrheology, hemostasis, vascular integrity, inflammatory cell function, and the magnitude and duration of intravascular volume expansion are influenced to varying degrees by the different fluids. There are extensive clinical data describing the effects of different solutions on these variables. However, only very limited large-scale studies have been conducted to distinguish between the effects of the different classes of fluid on patient outcomes, and the available data are inconclusive.

Many of the effects of different fluid solutions are governed by their distribution within the physiological compartments of the body. The following model, although simplistic, is conceptually useful.

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Fluid Compartment Physiology

Total body water for a 75-kg individual is approximately 45 L (60%). Two-thirds of this (30 L) is intracellular water. The remaining third (15 L) in the extracellular compartment is divided between the intravascular (3 L) and extravascular (12 L) compartments (Fig. 1). The total intravascular volume (or blood volume) is approximately 5 L and has intracellular (red and white cells and platelets: 40% [2 L]) and extracellular (plasma: 60% [3 L]) components. Plasma is a solution in water of inorganic ions (predominantly sodium chloride), simple molecules such as urea, and larger organic molecules such as albumin and the globulins.

The cell wall separates the intracellular compartment from the extracellular compartment. The capillary endothelium and the walls of arteries and veins divide the extracellular compartment into the intravascular and the interstitial (tissue or extravascular) compartments. Water moves freely through cell and vessel walls and is distributed throughout all these compartments. The energy-dependent Na^+/K^+ adenosine triphosphatase in cell walls extrudes Na^+ and Cl^- and maintains a sodium gradient across the cell membrane: Na^+ is an extracellular ion. The capillary endothelium is freely permeable to small ions such as

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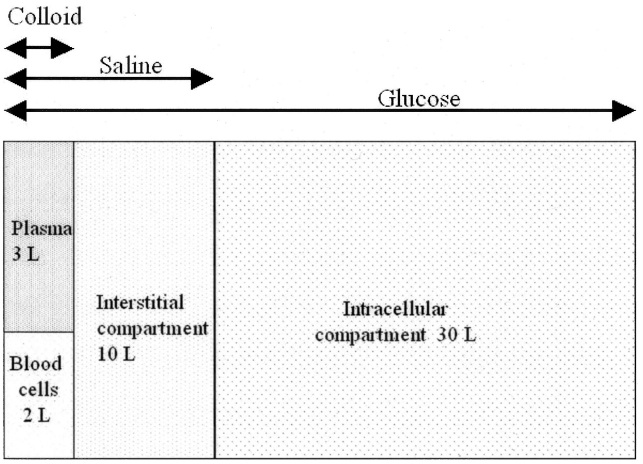

Figure 1. Model for volumes of distribution of isotonic colloid, saline, and glucose solutions.

Na^+ and Cl^- but is relatively impermeable to larger molecules such as albumin and the semisynthetic colloids, e.g., gelatins and starches, which are therefore normally theoretically maintained in the intravascular space.

This model is perturbed by a number of factors during anesthesia and surgery. Patients present for surgery with a variety of conditions that result in altered fluid distribution. Water and solute depletion may occur because of either decreased intake (e.g., fasting before surgery, anorexia, or altered conscious level) or increased losses (e.g., diarrhea, vomiting, or pyrexia). Many anesthetic drugs (e.g., IV induction drugs and volatile anesthetics) cause vasodilation, leading to a reduction in the ratio between the circulating volume and the capacity of the intravascular space, or myocardial impairment, leading to a reduction in flow through the circulation. Fluid shifts between compartments may also reduce the circulating volume (third-space losses and loss of intravascular fluid into the interstitium because of altered endothelial permeability in sepsis and inflammatory states; see below).

The Starling equation describes the movement of fluid across the capillary endothelium:

$$J_V \propto [(P_c - P_i) - \sigma(\pi_c - \pi_i)]$$

where J_v indicates transcapillary fluid flux, P_c indicates capillary hydrostatic pressure, P_i indicates interstitial hydrostatic pressure, π_c indicates intravascular oncotic pressure, π_I indicates interstitial oncotic pressure, and σ is the reflection coefficient.

In health, the net intracapillary pressures are more than the interstitial pressures, and this results in a pressure gradient that produces a slow continuous flow of fluid from capillary lumen to interstitium. This tissue, or interstitial fluid, drains via the lymphatic system back into the systemic circulation. In disease, all these factors can be altered, often resulting in an increase in the loss of fluid from the circulation.

Increased vascular permeability due to inflammatory activation with impairment of endothelial cell function can occur for a variety of reasons during major surgical procedures. Specifically, surgical tissue trauma, tissue hypoperfusion due to inadequate fluid therapy, ischemia/reperfusion injury, sepsis (local or blood-borne), and the use of extracorporeal circulations (e.g., cardiopulmonary bypass circuit) are recognized as inflammatory stimuli that can compromise vascular integrity. These changes are characterized by a reduction in the reflection coefficient (σ) that causes an increase in transcapillary fluid flux (J_v). Colloid molecules will be lost from the intravascular space, thus reducing the plasma volume expansion (PVE) effect of endogenous (albumin and globulins) and infused colloids. Collection of colloid molecules in the extravascular compartment causes an increase in interstitial oncotic pressure that further increases transcapillary flux toward the interstitium and favors the development of tissue edema. Larger colloid molecules have a higher reflection coefficient and are more likely to be maintained in the circulation and sustain intravascular volume expansion when vascular permeability is increased. In animal models, there is evidence that some of the semisynthetic colloids cause a decrease in colloid transcapillary escape rate and so minimize reductions in intravascular volume (see below).

Third-space losses are fluid that is lost into the transcellular fluid spaces. These losses occur into spaces, such as the bowel lumen and peritoneal and pleural cavities, which normally contain minimal volumes of fluid. However, there is a potential space that, in the presence of inflammation and breakdown of normal fluid compartment integrity, can fill up with nonfunctional extracellular fluid (1). The losses are predominantly from the interstitial compartment but must in turn be replaced from other compartments. Although third-space fluids may be reabsorbed over days or weeks, acutely they are equivalent to external loss of fluid, such as hemorrhage or evaporative loss. Third-space losses are common in association with the inflammatory response to burns, trauma, and surgery; they are a particular problem during major intraabdominal surgery and may exceed 10 $mL \cdot kg^{-1} \cdot h^{-1}$. These losses have been demonstrated with segmental bioelectrical impedance analysis during major surgery (2) and are increased after IV fluid therapy (3).

A solute in a solution generates an osmotic pressure that is proportional to the number of molecules or ions of solute and their charge characteristics: osmotic pressure is independent of solute molecular size. Osmotic pressure is generated only across semipermeable membranes, e.g., capillary endothelium and cell

wall. Water is "pulled" along osmotic gradients toward the larger concentration of solutes to maintain isotonicity in all compartments: solute distribution determines the water content of each compartment and is in turn determined by the properties of the membranes separating the compartments. Solutes that can pass freely across a semipermeable membrane do not generate any osmotic pressure—they are effectively a component of the solvent with respect to that membrane.

The volume of distribution of infused fluids is therefore dictated by their solute content. In turn, the PVE effect is directly related to the volume of distribution:

$$\text{Plasma volume expansion} = \frac{\text{Volume infused}}{\text{Volume of distribution}}$$

Assuming a closed model, infusion of water will expand all compartments in proportion to their total volume. Only 7% (intravascular fluid volume/total body water = 3 L/45 L) of the infused water would therefore remain in the intravascular space. However, infusion of water is an irritant to veins because of its hypotonicity. Infusion of isotonic glucose solution (5% glucose) is rapidly equivalent to infusion of water, because the glucose is rapidly metabolized, leaving water, which behaves as described above. Infusion of isotonic crystalloid (e.g., 0.9% NaCl or lactated Ringer's solution) will expand all the components of the extravascular volume, and 20% (intravascular fluid volume/extracellular volume = 3 L/12 L) of the volume infused will remain in the intravascular space. Infusion of an "ideal colloid," containing large molecules that do not escape from the circulation, will expand the intravascular volume by 100% of the volume infused.

To rationally prescribe fluid replacement, it is important to identify which compartment is depleted: specific losses should be replaced with the appropriate fluid. In acute emergency resuscitation, the first priority is restoration of an adequate circulating volume, and in this context adequate volumes of either colloids or crystalloid will be effective. Prolonged cavity surgery with significant evaporative losses would additionally require replacement of water in the form of 5% glucose.

Types of Fluid

IV fluids may broadly be classified into colloid and crystalloid solutions. They have very different physical, chemical, and physiological characteristics (Tables 1 and 2).

Crystalloid Solutions

Solutions of inorganic ions and small organic molecules dissolved in water are referred to as *crystalloids*. The main solute is either glucose or sodium chloride (saline), and the solutions may be isotonic, hypotonic, or hypertonic with respect to plasma. Isotonic saline has a concentration of 0.9% wt/vol (containing 0.9 g of NaCl in each liter of water). Potassium, calcium, and lactate may be added to more closely replicate the ionic makeup of plasma (Table 1). Crystalloids with an ionic composition close to that of plasma may be referred to as "balanced" or "physiological."

Glucose solutions are available as isotonic (5% w/v containing 50g glucose in each liter of water) or hypertonic (25% and 50% w/v) solutions. The small amount of glucose in the isotonic solution is rapidly metabolized, thus allowing the solvent water to freely distribute throughout total body water. Isotonic glucose solution should be prescribed to treat simple dehydration and provide water replacement. The hypertonic glucose solutions are given to provide glucose as a metabolic substrate in hypoglycemia or in combination with insulin therapy.

Colloid Solutions

A colloid is a homogeneous noncrystalline substance consisting of large molecules or ultramicroscopic particles of one substance dispersed through a second substance. The particles do not settle and cannot be separated out by ordinary filtering or centrifuging as can those of a suspension such as blood. Colloid solutions used in clinical practice for fluid therapy are divided into the semisynthetic colloids (gelatins, dextrans, and hydroxyethyl starches (HES)) and the naturally occurring human plasma derivatives (human albumin solutions, plasma protein fraction, fresh frozen plasma, and immunoglobulin solution). Most colloid solutions are presented with the colloid molecules dissolved in isotonic saline, but isotonic glucose, hypertonic saline, and isotonic balanced or "physiological" electrolyte solutions are also used.

Colloid molecular size can be highly variable. The semisynthetic colloids and the various preparations of plasma proteins in solution (fresh frozen plasma, plasma protein fraction, and so on) have a wide distribution of molecular sizes and are described as polydisperse. Human albumin solution contains more than 95% albumin with a uniform molecular size and is described as "monodisperse." The size/weight relationship is in most cases relatively constant, although some colloids of equivalent molecular weight (MW) can have different molecular sizes (e.g., succinylated and urea-linked gelatins have similar MW, but the succinylated product is physically larger because of increases in the negative charge causing a conformational change). Colloid MW can be described as the weight-averaged MW (the number of molecules at each weight multiplied by the particle weight divided

Table 1. Comparison of Composition and Osmolarity of Crystalloid Solutions for IV Administration

Solution	Osmolarity (mOsm/L)	Na^+ (mmol/L)	Cl^- (mmol/L)	K^+ (mmol/L)	Ca^{2+} (mmol/L)	Glucose (mg/L)	HCO_3^- (mmol/L)	Lactate (mmol/L)	Energy (kcal/L)
Glucose 5%	252	—	—	—	—	50	—	—	400
Glucose 25%	1260	—	—	—	—	250	—	—	2000
Glucose 50%	2520	—	—	—	—	500	—	—	4000
Sodium chloride 0.9%	308	154.0	154.0	—	—	—	—	—	—
Sodium chloride and glucose	264	31.0	31.0	—	—	40	—	—	320
Ringer's solution	309	147.0	156.0	4.0	2.2	—	—	—	—
Compound sodium lactate[a]	278	131.0	111.0	5.0	2.0	—	—	29.0	—
Plasmalyte B	298.5	140	98	5	—	—	50	—	—
Normasol[b]	280	140	98	5					

[a] Hartmann's solution or lactated Ringer's solution.
[b] Normasol contains acetate 27 mmol/L and gluconate 23 mmol/L.

Table 2. Comparison of Composition of Colloid Solutions for IV Administration

Solution	Colloid	MWw (Da)	MWn (Da)	Degree of substitution	Na^+ (mmol/L)	Cl^- (mmol/L)	K^+ (mmol/L)	Ca^{2+} (mmol/L)	Mg^{2+} (mmol/L)	Glucose (mg/L)
Gelofusine (4%)	Succinylated gelatin	30,000	22,600	—	154	125	—	—	—	—
Haemaccel (3.5%)	Polygeline	35,000	24,300	—	145	145	5.1	6.25	—	—
Voluven	Tetrastarch	130,000	60,000	0.4	154	154	—	—	—	—
Pentaspan	Pentastarch	264,000	63,000	0.45	154	154	—	—	—	—
HAES-steril 6% or 10%	Pentastarch	200,000	60,000	0.5	154	154	—	—	—	—
EloHase 6%	Hexastarch	200,000	60,000	0.6	154	154	—	—	—	—
Hespan 6%	Hetastarch	450,000	70,000	0.7	150	150	—	—	—	—
Hextend	Hetastarch	670,000	70,000	0.7	143	124	3	5	0.9	99
Gentran 40	Dextran 40	40,000	25,000	—	154	154	—	—	—	
Gentran 70	Dextran 70	70,000	39,000	—	154	154	—	—	—	—
Rheomacrodex	Dextran 40	40,000	25,000	—	154	154	—	—	—	—
Macrodex	Dextran 70	70,000	39,000	—	154	154	—	—	—	—

MWw = weight averaged mean molecular weight; MWn = number averaged mean molecular weight.

by the total weight of all the molecules) or number-averaged MW (the arithmetic mean of all particle MWs). The pattern of weight distribution can also be described by the ratio of the osmotic activity of a colloid solution across membranes with different pore sizes: the colloid oncotic pressure ratio (4).

Gelatins

Gelatins are prepared by hydrolysis of bovine collagen. Succinylated gelatin (Gelofusin™) is produced by enzymatic alteration of the basic gelatin peptide and is presented in a carrier solution with 154 mmol of sodium and 120 mmol of chloride ions. Succinylation causes a conformational change that increases molecular size without significantly increasing MW (5). Urea-linked gelatin (polygeline; Hemaccel™) is produced by thermal degradation of the raw material to small peptides (12,000–15,000 Da) followed by urea cross-linking to produce polymers of approximately 35,000 Da (5) and is presented in an isotonic solution of sodium chloride with 5.1 mmol/L potassium and 6.25 mmol/L calcium (6). Because of the significant calcium content of Hemaccel, blood should not be infused through a giving set that has been previously used for this product.

Concerns have been raised about the risks associated with bovine-derived gelatin because of the association between new-variant Creutzfeldt-Jakob disease and bovine spongiform encephalitis (BSE). All reported cases implicate bovine-derived food products and there are no known cases of transmission involving pharmaceutical gelatin preparations. Most clinicians continue to use bovine gelatin–based products; however, given the uncertainties concerning the transmission and behavior of BSE, awareness of this issue is important (7–9).

Dextrans

Dextrans are biosynthesized commercially from sucrose by *Leuconostoc* bacteria with the enzyme dextran sucrase (5). The resulting high-MW dextrans are then cleaved by acid hydrolysis and separated by repeated ethanol fractionation into a final product with a restricted MW range. The products of this process are D-glucose polymers joined largely by α-1,6 bonds into predominantly linear macromolecules. They are defined by their number-averaged MW: dextran 40 and dextran 70 have number-averaged MWs of 40,000 and 70,000 Da, respectively (10). Dextrans are polydisperse, and clearance is dependent on MW. Dextran

molecules of <50 to 55,000 Da are freely filtered at the renal glomerulus, and approximately 70% of an administered dose of dextran 40 will be excreted into the urine within 24 h. Larger molecules are excreted through the gut or metabolized by endogenous dextranases in reticuloendothelial cells (11). It is important to consult manufacturers' datasheets for recommended maximum doses, because these differ among products and geographical locations.

HES

Hetastarch (HES) are synthesized from amylopectin, a branching D-glucose polymer derived from maize or sorghum. Hydroxyethyl substitution by ethylene oxide occurs in the presence of an alkaline catalyst. Most substitutions occur at carbon 2 in the glucose ring; a few occur at carbons 3 and 6, and a higher C2/C6 substitution ratio results in slower enzymatic degradation (12). Hydroxyethylation slows hydrolysis by nonspecific α-amylases in the blood; unsubstituted starch molecules are rapidly metabolized. The degree of substitution (DS), expressed as a number between 0 and 1, describes the proportion of substituted to nonsubstituted glucose moieties, and an increased DS confers greater resistance to hydrolysis. The final product is produced by hydrolysis of the substituted starch to the required MW, followed by a purification process. Fractionation to produce narrower MW bands is used for some products. The MW profile and DS define the individual products. HES products can be divided into three classes by their weight-averaged MW: high MW (450–480 kDa), medium MW (approximately 200 kDa), and low MW (70–130 kDa). Examples of commercially available starches are 6% high-MW hetastarch in saline (Hespan™), 6% high-MW hetastarch in balanced electrolytes (Hextend™), medium-MW pentastarch in saline (Pentaspan™, EloHAES™, HAES-steril™), and low-MW tetrastarch in saline (Voluven™). Acetyl starch products are currently undergoing clinical testing. It is important to consult manufacturers' datasheets for recommended maximum doses, because these differ among products and geographical locations. Table 2 outlines a comparison of the contents of colloid solutions for IV administration.

Properties of Colloids

The semisynthetic colloids are a heterogeneous group of products, and each product has a defined set of properties. They vary in the magnitude and duration of PVE, effects on hemorrheology and hemostasis, interaction with endothelial and inflammatory cells, adverse drug reactions, and cost.

The duration of PVE produced by each colloid is governed by the rate of colloid molecule loss from the circulation and by their metabolism. The rate of loss through the capillary endothelial barrier into the interstitial space and through the renal glomerulus into the urine is determined by molecular size (and, therefore, weight) and surface charge characteristics. The rate of intra- and extravascular metabolism is governed by specific chemical qualities of molecules (e.g., HES C2/C6 ratio and resistance to hydrolysis). The most useful descriptors of magnitude and duration of PVE are the intravascular half-life and the fraction of administered volume retained in the circulation after a specific time. Ninety minutes after the administration of 1 L, the gelatins produce a PVE of approximately 0.2 L (equivalent to crystalloid), whereas dextran and HES preparations produce a PVE of 0.7–0.8 L (13).

The predominant effect of colloid solutions on blood rheology (the physics of flow and deformation of matter) is to reduce whole blood viscosity by simple hemodilution, thus improving blood-flow characteristics (14). The magnitude of this effect is proportional to the degree of PVE and is therefore larger initially for the lower-MW (30,000–40,000 Da) HES and dextran products that produce a large initial increment in intravascular volume and, therefore, a larger hemodilution effect. Independent of this dilutional decrease in whole blood viscosity, semisynthetic colloids also influence plasma viscosity and red cell aggregation, and this contributes to their overall effect on whole blood rheology. The higher-MW dextrans and HES cause an increase in plasma viscosity, and the larger dextrans (e.g., dextran 70) and gelatins also tend to cause red cell aggregation (15). These effects are smaller in magnitude than the dilutional decrease in whole blood viscosity, but investigators are divided as to whether blood flow and tissue oxygenation can be compromised (15,16). The lower-MW dextrans (e.g., dextran 40), starches, and human albumin solution tend to cause reduced red blood cell aggregation and plasma viscosity (15,17), and this further enhances dilutional hypoviscosity and results in increased flow, particularly in the venous system.

All of the semisynthetic colloids affect hemostasis. This occurs partly as a result of simple hemodilution of clotting factors and partly because of colloid-specific effects on components of the hemostatic mechanism. There is also increasing evidence that crystalloid hemodilution can induce a hypercoagulable state, but the clinical significance is uncertain (18,19). The gelatins appear to have the least effect on hemostasis; however, some abnormalities have been noted over and above simple hemodilution of clotting factors. Gelatin use has been associated with reduced levels of von Willebrand factor (vWF) and factor VIIIc, and studies with the thromboelastograph (TEG™) (20) and sonoclot (21) technology suggest that clot strength may be reduced after large-volume gelatin infusions. However, there is little evidence that this results in increased blood loss or adverse bleeding events (22).

HES solutions have varying effects on hemostasis that are dependent on the MW of the HES molecule (23). Although conventional clotting indices are unaffected at high MW, HES products in particular have been reported to produce a coagulopathy, and this is thought to be associated with increased blood loss after surgery (22–24). Impaired platelet function, a von Willebrand-like syndrome with reduced vWF and factor VIIIc, and impaired coagulation measured with the TEG™ have been reported and may explain these clinical findings (25,26). Medium- and low-MW HES preparations have been shown to produce similar, but lesser, effects compared with the higher-MW products, and it is believed that the risk of increased blood loss is minimal with these products (23,27). The dextrans are associated with more significant hemostatic derangements (28,29) and are effective antithrombotic agents (28,30,31). In addition to simple hemodilution of clotting factors, low-MW dextrans increase microvascular flow by platelet disaggregation and have specific effects on several components of the hemostatic system (32). Factor VIIIc and vWF are reduced, as is factor VIII activity (22). Red cell aggregation is also reduced with the lower-MW dextrans. In patients whose hemostatic function is normal before infusion, a maximum dose of 1.5–2 g/kg is often recommended to avoid the risk of bleeding complications.

Dextran and HES molecules may also have specific antiinflammatory effects, including reducing postischemic leukocyte-endothelial interactions and platelet adhesiveness (11). In general, the effect is stronger for dextran preparations, although pentastarch (HES pentafraction) is thought to exert more pronounced inhibition of endothelial cell activation and neutrophil adhesion. Pentafraction is also believed to have specific benefits in retaining fluid within the capillaries, probably by physically plugging endothelial pores, in situations in which capillary leak occurs (33).

Anaphylaxis or anaphylactoid events have been described in association with all of the semisynthetic colloids and albumin. The incidence of severe reactions (life-threatening events; e.g., shock, life-threatening smooth muscle spasm, or cardiac or respiratory arrest) is probably more frequent for gelatins (most frequent reported incidence <0.35%) and dextrans (<0.28%) than for albumin (<0.1%) or HES (<0.06%) (14). The advent of dextran 1 hapten treatment has significantly reduced the risk of dextran-related anaphylactic events to <0.0015% (34). In comparison, the rate of serious reactions to penicillin is of the order of <0.05%. A significant incidence of itch has been noted with HES products by some authors (35).

Crystalloids Versus Colloids

There is a long-standing controversy between crystalloid and colloid enthusiasts relating to the relative merits of the two fluid classes. The arguments center around the increase in edema associated with crystalloid therapy and the known adverse effects (hemostatic impairment, anaphylaxis, and so on) associated with colloid use. Significant PVE requires large-volume crystalloid infusion. This causes a significant expansion of the extracellular volume that leads to tissue edema. Large-volume crystalloid resuscitation after major burns is associated with significant tissue edema when compared with colloid resuscitation (36). Theoretically this will result in increasing diffusion distances within tissues, and compression of small vessels and capillaries results in compromised end-organ perfusion and oxygenation. Animal studies demonstrate that crystalloid infusion is associated with significant tissue fluid accumulation (37,38), but it is unclear whether this is more than that which occurs after colloid administration (39,40).

Similarly, data on whether tissue oxygen extraction is altered by accumulation of interstitial fluid are inconclusive, with evidence supporting (37,41) and refuting (42) this proposition. Katrin et al. (43), in an abdominal surgery model, recently showed that colloid resuscitation was associated with an increase in perioperative tissue oxygen tension, whereas this decreased in patients who were resuscitated with crystalloid. Prien et al. (44) demonstrated that, in patients undergoing Whipple's procedure, crystalloid resuscitation with lactated Ringer's solution (LR, Hartmann's solution) resulted in a significant increase in the water content of a jejunal specimen compared with intraoperative resuscitation with hetastarch or albumin. Intestinal edema has been associated with impaired gastrointestinal function tolerance for enteral nutrition (45,46), an increased potential for the development of bacterial translocation, and the development of multiple organ dysfunction syndrome (47,48). Many randomized controlled trials (RCTs) have been conducted to compare colloid and crystalloid fluid therapy in a variety of clinical settings, although none has focused on mortality as an end-point. Three systematic reviews have focused specifically on this issue (49–51). Meta-analyses from the first two reviews suggested an increase in mortality associated with colloid use, but the most recent analysis reported that "methodologic limitations preclude any evidence-based clinical recommendations" and proposed large carefully designed RCTs to directly address this question. Most clinicians, in the absence of clear guidance from the available literature, use a combination of crystalloid and colloid fluid therapy. Evidence suggests that colloid resuscitation may result in less edema and better quality of recovery in the postoperative period. Specifically, these patients had less frequent nausea and vomiting and severe pain, which could be explained by the lower degree of tissue edema (52).

Balanced Versus Unbalanced Fluids

Large-volume administration of 0.9% saline and of colloids dissolved in isotonic saline is associated with the development of hyperchloremic metabolic acidosis due to the high chloride load (53–55). Balanced or physiological fluids that contain inorganic ions (calcium, potassium, or magnesium), molecular glucose, or buffer components, such as bicarbonate or lactate, and that have a smaller chloride concentration are not associated with the same disturbance of acid/base physiology (53–56). Data suggest that this acidosis may be clinically significant. Patients randomized to balanced solutions, when compared with those randomized to saline-based fluids, had less impairment of hemostasis (52) and improved gastric perfusion (55). Renal function may also be better preserved (55). Balanced crystalloid solutions have been available for many years (e.g., Hartmann's solution/Ringer's lactate). Colloid solution presented in a "balanced" form (e.g., Hextend; 6% HES in a balanced electrolyte solution) are now becoming widely available (52,55).

Albumin and Plasma Protein Fraction

The use of human-derived colloid has a number of significant disadvantages, including expense and the theoretical risk of transmission of infectious agents such as new-variant Creutzfeldt-Jakob disease, which is associated with BSE. A systematic review of human albumin in the critically ill suggested that administration might increase mortality (57). However, this analysis was widely criticized for the heterogeneity of the included studies. In most countries, the use of albumin in the management of hypovolemia is relatively uncommon because the semisynthetic colloids are believed to be at least as effective. Recent reports from a 7000-patient multicenter RCT of critically ill patients in Australia suggested that there was no difference in mortality between patients managed with albumin or 0.9% NaCl (58).

Hypertonic Fluids

In recent years, hypertonic (600–1800 mOsm/L) crystalloid and colloid solutions have been introduced for certain clinical indications. The theoretical advantage of these solutions is that a small volume of administered fluid will provide a significant PVE. The high osmolarity of these solutions draws tissue fluid into the intravascular space and thus should minimize tissue edema for a given plasma volume increment. In the perioperative setting, literature on use in humans is limited (59–61). Hypertonic crystalloids and colloids presented in a hypertonic saline carrier have been shown to achieve adequate resuscitation in a number of clinical settings. A smaller volume of hypertonic solution is normally required to achieve similar PVE. In particular, these solutions are thought to result in reduced cerebral edema in patients who are at risk of this complication, and indeed, these solutions may have a place in treating refractory cerebral edema. Outside the perioperative arena, they are finding use in the management of burn patients and in prehospital resuscitation of trauma victims (62). They are limited at present to single-dose administrations. However, hypertonic solutions are often considered to be irritants to veins because of their high osmolarity, and it is recommended that they be given into large veins or centrally, although the evidence base for this advice is sparse. A limited study using 7.5% saline/6% dextran 70 failed to demonstrate any vessel damage after brief (2 min), rapid infusion through the cephalic vein or femoral artery (63). However, 11.7% saline, which is the minimum effective concentration for use clinically as a sclerosing agent (64), has been demonstrated to cause immediate clinical and histological endothelial damage and thrombosis when infused into small veins in animal models (65). Parenteral nutrition solutions up to 3 times normal osmolarity seems to be readily tolerated by peripheral veins (66), thus suggesting that the weaker hypertonic solutions (e.g., 1.8% saline) can safely be administered peripherally.

How Should Fluids Be Administered?

The second part of this review will discuss how fluids should be given. We believe that in many cases, fluids are administered without adequate monitoring to guide dosage (volume) and that this may result in adverse outcomes relating to either inadequate or excess fluid administration (see below). To justify this claim, we offer clinical data to support the notion that strategies of fluid administration by titration of dosage (volume) to rational physiological end-points by using appropriate monitoring can improve clinical outcome (see below). The small amount of available evidence suggests that in general, flow monitoring (measurement of cardiac output) is not often used perioperatively (67,68).

Adverse outcomes may be associated with inadequate or excessive fluid administration. Inadequate fluid administration can lead to a reduced effective circulating volume, diversion of blood toward vital organs (brain and heart) and away from nonvital organs (gut, skin, and kidneys), and inadequate tissue perfusion of the nonvital organs. A comparison of "conservative" ($8\ mL \cdot kg^{-1} \cdot h^{-1}$) and "aggressive" ($16–18\ mL \cdot kg^{-1} \cdot h^{-1}$) fluid administration strategies in 56 patients undergoing colonic resection demonstrated improved tissue oxygen tensions measured

with a polarographic sensor implanted subcutaneously, and improved capillary blood flow was evaluated after surgery with a thermal diffusion system (69). In a study comparing "standard of care" with a strategy of fluid challenges to increase left ventricular stroke volume measured by esophageal Doppler aortic velocimetry, gut perfusion measured with gastric tonometry was improved, and complications were reduced (70). This finding supports the hypothesis that improving tissue perfusion may also result in reduced inflammatory activation and, hence, organ dysfunction. Other studies have demonstrated that inadequate tissue perfusion measured with gastric tonometry is associated with adverse perioperative outcome (71,72).

Conversely, excessive administration of fluid may result in adverse effects. Excess fluid in the intravascular compartment leads to increased pressure in the venous circulation and results in loss of fluid from the intravascular space into the interstitial (extracellular) space. This leads to the development of pulmonary and peripheral edema and consequent compromise of systemic and/or local tissue oxygenation. Pulmonary edema is clearly a major adverse outcome that results in an increase in the alveolar-arterial oxygen gradient and systemic hypoxia. However, it is interesting to note that infusion of 40 mL/kg of lactated Ringer's solution in healthy volunteers led to a significant decrease in pulmonary function (presumably secondary to subclinical pulmonary edema) but had no effect on exercise capacity when compared with controls (73).

The arguments as to whether tissue edema influences tissue oxygenation are presented in the section above comparing crystalloid and colloid effects. As noted above, there is evidence that intestinal edema is associated with impaired gastrointestinal function tolerance for enteral nutrition (45,46), an increased potential for the development of bacterial translocation, and the development of multiple organ dysfunction syndrome (47,48).

Fluid Administration Strategies and Clinical Outcomes

Studies comparing "drier" and "wetter" strategies of fluid administration are hard to interpret. The almost universal practice of preoperative oral fluid restriction to prevent aspiration of gastric contents, although not evidence based (74), ensures that patients routinely receive an anesthetic with a fluid deficit (75), and some fluid will almost certainly benefit all patients (see below). The balance between inadequate fluid resuscitation and decreased tissue perfusion and excess fluid with edema formation will vary for specific types of surgery. Patients' preprocedure volume status may vary, and different magnitudes of surgical insult require very different amounts of fluid therapy. Patients undergoing major bowel surgery who receive preoperative bowel preparation without fluid replacement have an increased preoperative fluid deficit; those randomized to bowel preparation with no additional fluids lose weight, have a postural decrease in arterial blood pressure, and have less urine output and increased creatinine when compared with those receiving crystalloid (mean of 2000 mL) (76), and these individuals are likely to benefit from correction of this deficit. Conversely, in the special case of plastic or maxillofacial flap surgery, in which edema is known to adversely affect flap outcomes, relatively conservative fluid therapy may produce better outcomes (77). It is therefore important to distinguish between different types of surgery, patients' conditions, and factors contributing to hypovolemia to balance the risks of tissue hypoperfusion and of pulmonary and peripheral edema.

The "Recipe Book" Approach

The traditional "recipe book" approach to fluid administration is based on the use of formulas based on a continuous predetermined rate of infusion of fluid with additional replacement of observed losses. This approach takes no account of preoperative fluid status, the known inaccuracy of observation of blood and other fluid losses, or perioperative variations in myocardial function and vascular tone. The following RCTs in which one group is administered more fluid than the other either as a fixed dose (e.g., 1000 mL) or dosed by weight (e.g., 100 mL/kg) are presented in approximate order of magnitude of surgical challenge. Half an hour of preoperative crystalloid infusion (20 mL/kg) in ambulatory gynecological surgery or intraoperative crystalloid infusion ($20\ mL \cdot kg^{-1} \cdot h^{-1}$), when compared with $2\ mL \cdot kg^{-1} \cdot h^{-1}$, improved outcome after mixed ambulatory surgery (78,79). Postoperative nausea and vomiting was reduced after intraoperative fluid therapy (1000 mL of crystalloid) when compared with controls who received no fluids in minor gynecological surgery (80).

Holte and Kehlet (81), in a review of the data on compensatory fluid administration to make up for preoperative losses relating to routine fasting, suggested that approximately 1000 mL leads to an improvement in clinical outcomes. However, a randomized study comparing a "dry" (approximately 400 mL/h) with a "wet" (approximately 1000 mL/h) strategy in radical head and neck surgery showed no difference in basic renal outcomes (82). In more major (in terms of physiological disturbance) surgery, patients undergoing colorectal resection were randomized to a "restrictive" strategy (maintenance of preoperative body weight) or a "standard" regimen (standard of care usually associated

with an increase of 3–6 kg body weight), and a reduced complication rate was observed in the restrictive group (83). Interesting information comes from studies of the strategy of targeting oxygen delivery goals ("optimization" or "goal-directed therapy") that developed out of Shoemaker et al.'s (84) observations that survivors of high-risk surgery often exhibited higher oxygen delivery and blood flow values than nonsurvivors. In a number of these studies in which the intervention group received fluid and inotropes according to specific goals, there was an improved outcome in the intervention group that received more fluid (85–87). However, in these complex studies, it is hard to untangle the complex interactions between elements of the intervention (fluids and inotropes), the setting in which the patients were cared for, and the monitoring used.

It appears from the limited data that some fluid is better than none, but as the magnitude of surgical insult becomes greater, choosing what fixed dose to give becomes harder. When significant amounts of fluid may be required for more major surgery, an alternative approach is more effective: the goal of maintenance of effective intravascular volume to maintain tissue perfusion and cellular oxygenation. This goal is both physiologically self-evident and supported by the data presented below. This approach involves the titration of fluids to physiologically relevant biometric end-points that can be monitored and responded to in the intraoperative setting. When compared with the "text book" recipe, this alternative approach results in improved outcomes in RCTs in major surgery (see below). How do we decide which end-points to choose? As discussed above, they should result in the avoidance of underuse of fluid therapy resulting in covert hypovolemia and inadequate tissue perfusion and the administration of excess fluid, with the attendant risks of pulmonary and peripheral edema. The following sections discuss the rationales and clinical outcome data relating to the potential physiological end-points that might be used to achieve this goal.

Intravascular Pressure Measurement

There is no evidence to support the concept that use of static measurements of intravascular pressure achieves the goal of avoiding tissue under perfusion. For many years it has been recognized that arterial blood pressure measurements do not reflect blood flow (88) and that hypovolemia may be present despite normal systemic and filling pressures (89). Although a low arterial blood pressure indicates inadequate effective circulating volume, a normal arterial blood pressure does not exclude covert hypovolemia with reduced tissue perfusion. In a study involving healthy volunteers, removal of 20%–30% of the blood volume was undetectable with conventional hemodynamic observations, in particular, arterial blood pressure, but it produced significant impairment of tissue perfusion indices (89). There is clearly an arterial pressure below which specific organs, most notably the kidney and the brain, fail to function normally, and this pressure varies among individuals (90). Maintenance of mean arterial blood pressure above this level, which should be defined by reference to an individual's preoperative mean arterial blood pressure, should be a basic goal of any fluid resuscitation scheme. However, although this is necessary to prevent underperfusing whole organs (e.g., brain and kidney), it is not sufficient to ensure maintenance of tissue perfusion throughout the body. As highlighted above, covert hypovolemia can exist in the presence of a normal arterial blood pressure.

Measurements of central venous pressure (CVP) or pulmonary artery occlusion pressure (PAOP, pulmonary artery "wedge" pressure) have been used as indices of intravascular volume status. This approach is based on a number of flawed assumptions. Right- and left-sided filling pressures are believed to have a constant relationship to right and left ventricular end-diastolic volume (preload), respectively. However, the relationships among intravascular volumes, cardiac filling pressures, end-diastolic volumes, and endogenous vasopressor tone are probably too complex to model. Certainly, fluid management strategies based on simple filling pressure targets are less successful than those in which blood flow is targeted (91,92). Normal filling pressure for an individual varies with ventricular function; chronic ventricular impairment is associated with higher filling pressures (93). Additionally, we know that the pattern of filling pressure response to a fluid challenge is not predictable simply from that pressure: under different conditions an increased CVP or PAOP may decrease, increase, or remain the same in response to a fluid challenge (94,95). Preload (filling pressures or end-diastolic volumes) and afterload (systemic vascular resistance) are both influenced by several common factors: intravascular volume and vascular tone are both key determinants. Several vasoactive mediators (catecholamines, renin-angiotensin-aldosterone axis, and vasopressin) determine vascular tone in both venous and arterial systems. When levels of these mediators are high, causing increased vascular tone, PVE may result in a decrease in filling pressures and an increase in stroke volume and cardiac output. This is thought to be due to decreased drive from vasopressor reflexes causing a reduction in levels of circulating vasoconstrictors, with a resultant decrease in arterial and venous vascular tone.

Systolic and Pulse Pressure Variation

Several studies suggest that variations in systolic blood pressure and pulse pressure with positive pressure ventilation are a useful method of predicting circulatory responses to a fluid challenge. This technique formalizes the subjective assessment of "swing" in the arterial pressure trace with the respiratory cycle that has been empirically used as an indicator of hypovolemia for many years. Studies in patients with sepsis demonstrated that a decrease in systolic pressure of ≥5 mm Hg during one positive pressure mechanical breath was strongly predictive of a positive response to a subsequent colloid volume challenge (96) and that both systolic blood pressure variation and pulse pressure (systolic − diastolic) variation were able to predict the response to PVE, with pulse pressure variation being the most reliable indicator (97). Studies in surgery, however, have been less conclusive. Although systolic blood pressure variation has been shown to be related to stroke volume variation with positive pressure ventilation (98), the only published study assessing the utility of this approach in surgical patients did not demonstrate a relationship between systolic blood pressure variation and subsequent response to a fluid challenge in cardiac surgical patients before cardiopulmonary bypass (99).

The Fluid Challenge and Intravascular Pressure Measurement

Information may be gained by observing the response of CVP and/or PAOP to a fluid challenge (Fig. 2). A fixed volume of colloid (e.g., 200 mL) is infused over 10–15 min, and the response of CVP/PAOP is observed. CVP/PAOP may stay the same, decrease, or increase. No change in CVP/PAOP, or a decrease in pressure, after fluid challenge suggests covert hypovolemia and suggests that the fluid challenge should be repeated (Point A). The combination of an increase in intravascular volume without a related increase in pressure indicates that vascular compliance has increased, suggesting a reduction in vasoconstrictor tone. A sustained increase of ≥3 mm Hg suggests that the limits of intravascular compliance have been reached and that fluid challenges should be discontinued (Point B). This approach has been shown to improve outcome when compared with "routine practice" in the perioperative care of patients undergoing repair of fractured neck of the femur (100).

The Fluid Challenge and Measurement of Blood Flow

Five published studies have used intraoperative esophageal Doppler monitoring as an alternative method of acquiring information about blood flow. These studies

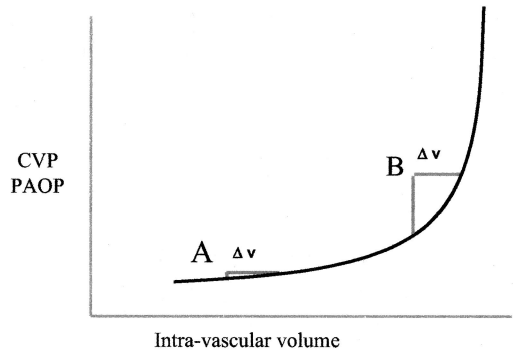

Figure 2. Schematic representation of the response of central venous pressure (CVP)/pulmonary artery occlusion pressure (PAOP) to an increase in intravascular volume.

have used algorithms using repeated boluses of semisynthetic colloid to maximize stroke volume, rather than targeting a specific figure, and compared this with standard fluid management. The conceptual relationship between intravascular volume and stroke volume is represented in Figure 3. A fluid challenge causing an increase in stroke volume (Point A) suggests that subsequent fluid challenges are unlikely to result in overfilling (ascending portion of the Frank-Starling curve). Conversely, no change (Point B) or a decrease in stroke volume (Point C) indicates that further fluid challenges are inappropriate: the likely result would be a decrease in ventricular performance. Infusion of fluid after this response will lead to increased volumes of infused fluids with no benefit. Fluid challenge with monitoring of stroke volume allows maximization of stroke volume without inappropriate excessive fluid infusion. In the first study, patients with normal left ventricular function undergoing coronary artery revascularization had a statistically significant reduction in the length of both intensive care unit and overall hospital stay in the protocol group (70). It is interesting to note that patients in the protocol group demonstrated improved gastrointestinal perfusion as determined by gastric tonometry. The second study, of patients undergoing repair of proximal femoral fracture, also demonstrated a reduction in hospital length of stay in patients randomized to the protocol group (101). Another study observing a similar group of patients compared a colloid fluid challenge approach titrated against CVP or esophageal Doppler (100). Time to being medically fit for discharge was reduced in the two protocol groups, but there was also a trend to increased mortality in these groups. A study using a similar algorithm in moderate-risk general surgical patients demonstrated an earlier return to tolerating solid food and a reduction in hospital stay in the protocol group (102) A further study in patients undergoing elective major bowel surgery suggested that use of a similar algorithm resulted in a reduction in the requirement

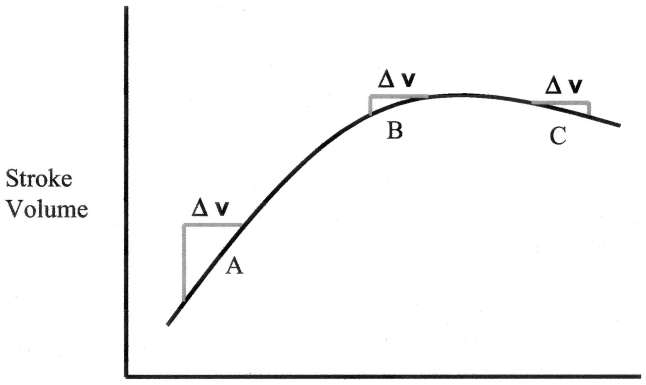

Figure 3. Schematic representation of the response of stroke volume to an increase in intravascular volume.

for postoperative critical admission (103). None of these studies was designed to demonstrate a mortality difference.

Measurement of Tissue Perfusion

Tissue perfusion indices as goals for resuscitation are intuitively very appealing when the ultimate goal of fluid therapy is the maintenance of tissue perfusion and cellular oxygenation. A number of technologies have been used to monitor perfusion perioperatively. Gastrointestinal tonometry (gastric and sigmoid) (104) and laser Doppler flowmetry (105) have been used to assess splanchnic perfusion. Microdialysis catheters (106), near-infrared spectroscopy (107), transcutaneous oxygen measurements (108), and tissue pH monitors (109) have all been used perioperatively to monitor local (surgical site) or general (distant site) tissue perfusion. However, no interventional study using one of these monitors to guide fluid therapy has demonstrated an improvement in outcome. The only monitor tested as part of an interventional study in the perioperative environment is the gastric tonometer. Two studies have failed to demonstrate a reduction in perioperative mortality by using tonometry-guided therapy, although both showed a trend toward mortality reduction (110,111). The intuitive appeal of being able to directly monitor tissue perfusion and use this information to guide fluid therapy has yet to gain support from clinical trial data. Work is continuing in this area, and this approach is likely to become increasingly important in the future.

Conclusion

Knowledge of the properties of the various available IV fluids should guide their administration. However, the available clinical outcome data (mortality and major morbidity) provide no evidence for the relative benefit between crystalloid and colloid fluid therapy or between the different types of colloid. Data are increasing to support the concept that physiologically balanced electrolyte composition results in better clinical outcomes (in particular, reduced incidence of impaired renal function and coagulopathy) when compared with saline-based fluids.

Correct dosage of fluid therapy improves patient outcome after surgery. Accurate dosing of fluid therapy in major surgery requires monitoring of arterial blood pressure and blood flow. There is an increasing amount of data supporting the notion that fluid therapy guided by left ventricular stroke volume improves outcome after a variety of different types of surgery.

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