Perioperative Fluid Management

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New concepts and practices of perioperative fluid management continue to evolve. Until the mid-to-late 1960s, rigid restriction was the prevailing strategy of perioperative fluid management (1). This review will focus on several areas of research that are changing clinical practice, including the following:

1. The kinetics of plasma volume expansion produced by IV fluids.
2. Recent developments in colloid solutions.
3. Specific components of available fluids.

The Kinetics of Plasma Volume Expansion Produced by Intravenous Fluids

Principles

Conventional prediction of plasma volume expansion (PVE) after fluid infusion assumes that retained fluid (infused fluid minus excreted fluid) is distributed, based on fluid composition, across physiologic fluid spaces (Table 1) and the Starling equilibrium, which governs the distribution of isonatremic, noncolloid fluids between PV and the ISF (the two components of ECV). The Starling equilibrium is defined as follows:

$$Q = kA[(P_c - P_i) + \sigma(\Pi_i - \Pi_c)]$$

where Q = fluid filtration, k = capillary filtration coefficient (conductivity of water), A = the area of the capillary membrane, P_c = capillary hydrostatic pressure, P_i = interstitial hydrostatic pressure, σ = reflection coefficient for albumin, Π_i = interstitial colloid oncotic pressure, and Π_c = capillary colloid oncotic pressure. The small proportion (<0.5%) of osmotic activity contributed by plasma proteins is essential in determining the equilibrium between IFV and PV. If serum osmolality is normal, total osmotic pressure exceeds 5400 mm Hg, only 24 mm Hg of which is colloid osmotic (oncotic) pressure.

The following equation predicts the static effects of fluid infusion on PVE:

$$PVE = \text{volume infused} \times (PV/V_D)$$

where V_D = distribution volume (Table 1). For example, how much would PVE increase as a consequence of infusion of 500 mL of 5% dextrose in water? In a 70-kg individual, PV is approximately 3.0 L. Because the infused volume is sodium-free, the V_D is TBW (equal to 60% of total body weight, or 42 kg in a 70-kg individual). Therefore, PVE = 500 mL × (3/42) or 36 mL. Infusion of 500 mL of lactated Ringer's solution (LRS) or 0.9% saline, for which V_D = ECV (20% of total body weight or 14 kg in a 70-kg individual), would result in PVE = 500 mL × (3/14) = 107 mL. If capillary membrane permeability is normal, fluids containing colloids such as albumin, dextran, or hydroxyethyl starch (HES) preferentially expand PV rather than IFV or ICV. Each gram of intravascular albumin holds 14 to 15 mL of water in the PV (2). Therefore, 500 mL of 5% albumin, containing 25 g albumin, would expand PV by approximately 375 mL.

Hyperosmotic fluids, e.g., 7.5% saline, increase venous return primarily by translocating intracellular fluid into PV (3). However, hypertonic saline infusions also transiently increase ECV through osmotic attraction of fluid from the IFV into the PV. Addition of hyperoncotic colloid to the hypernatremic fluid will increase the PV increment.

Kinetic analysis of PVE replaces static assumptions with dynamic data and serves the same purposes as pharmacokinetic analysis of drug concentrations, e.g., estimating peak effects and rates of clearance. Both the effects of a bolus of fluid on PVE and the rates of infusion necessary to maintain any given level of plasma dilution can be predicted by kinetic modeling (4). However, because infusion of fluid does not introduce a novel substance that results in a measurable concentration, the effects of fluid infusion on PVE must be inferred from changes in the concentrations of other variables. Svensén and Hahn (5) evaluated three endogenous tracers, blood water concentration, serum albumin concentration, and total hemoglobin (Hb), in eight volunteers who received bolus infusions of acetated Ringer's solution, 6% dextran 70, or 7.5% saline. Hb concentration provided simple, reproducible measurements (Fig. 1).

After infusing the test fluids, Svensén and Hahn (5) used nonlinear regression of fluid-induced changes in

Table 1. Fluid Distribution Volumes

Description	% Total Body Weight	Volume (L/70 kg body weight)
Total body water	60	42
Intracellular volume	40	28
Extracellular volume	20	14
Interstitial fluid volume	16	11
Plasma volume	4	3

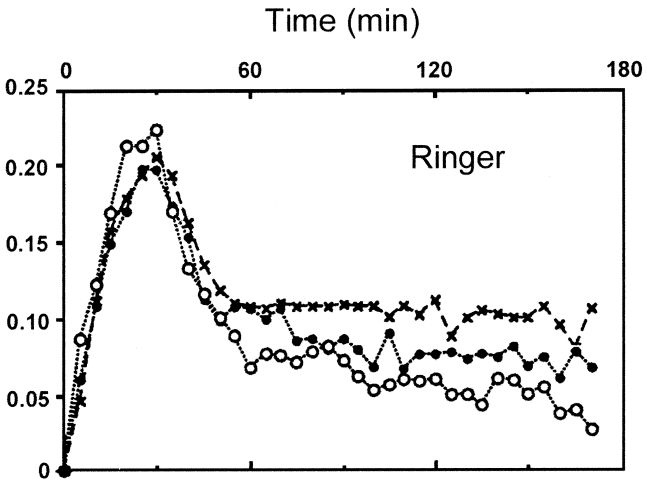

Figure 1. The blood hemoglobin (B-hemoglobin, closed circles line), blood water (B-water, open circles line), and serum albumin (S-albumin, X line) concentrations used as markers to indicate the dilution of the plasma volume during IV infusion of 25 mL/kg of lactated Ringer's solution over 30 min in 8 male volunteers. Data are mean values; correction for blood sampling was not made. Note that in normovolemic, unanesthetized volunteers a substantial bolus of isotonic crystalloid (equivalent to 1750 mL in a 70-kg person) produces a modest peak in volume expansion that rapidly decreases. Modified from Svensén et al. (5) with permission of the publisher.

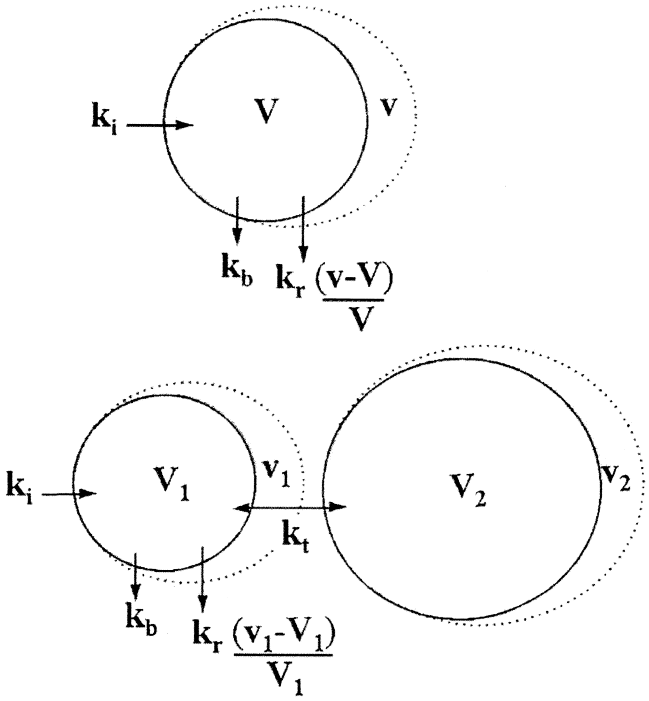

Figure 2. Schematic drawing of the kinetic model used to calculate the size of the body fluid spaces expanded by IV infusions of fluid in humans. Data are fitted to a one- or two-volume-of-fluid-space (VOFS) model. The assumptions underlying the one-compartment VOFS model (top) are as follows: 1) during fluid infusion, fluid enters an expandable space of volume v at a constant rate k_i; 2) the expandable fluid space has a target volume V, which the body strives to maintain; 3) volume v changes by fluid being eliminated from the fluid space at a basal rate, k_b (perspiration and basal diuresis), and at a controlled rate. The controlled rate is proportional by a constant k_r to the relative deviation of v from the target volume V. The assumptions behind the two-compartment VOFS model (bottom) are similar: 1) during fluid infusion, fluid enters an expandable space of volume v_1 at a constant rate k_i; 2) there is a secondary expandable fluid space of volume v_2 exchanging fluid with the primary fluid space; 3) volume v_1 changes through exchange with the secondary fluid space and as a result of fluid being eliminated from the primary fluid space at a basal rate, k_b (perspiration and basal diuresis), and at a controlled rate. 4) The primary and secondary fluid spaces have target volumes V_1 and V_2 that the system strives to maintain by acting on the controlled elimination mechanism k_r, which is proportional to the relative deviation from the target volume of the primary fluid space, and by acting on the fluid exchange mechanism; 5) the net rate of fluid exchange between the two spaces is proportional to the difference in relative deviations from the target volumes by a constant k_t. From Svensén et al., (5) with permission of the publisher.

Hb concentration to categorize mathematically clearance curves as one- and two-volume-of-fluid-space (VOFS) models (Fig. 2). These volumes of fluid space do not correspond precisely to anatomic or physiologic spaces (much as pharmacologic volumes of distribution often do not correspond precisely to physiologic spaces). Certainly, the most striking aspect of these data was the small proportion of crystalloid remaining in the vascular tree after equilibration.

Ultimately, kinetic analysis should be useful in clarifying the interaction between the kinetics of fluid administration and the effects of hemorrhage, trauma, anesthesia, and surgery on surgical fluid requirements. For instance, after mild hemorrhage in conscious volunteers, a greater proportion of infused isotonic crystalloid remained in the vascular tree than after fluid infusion in normovolemic volunteers (6), perhaps because transcapillary flux of IF augments fluid retention. In sheep anesthetized with isoflurane, infused crystalloid fluid was lost from PV as rapidly as in conscious sheep; however, the fluid appeared to accumulate in the interstitium rather than being excreted in the urine (7). Subsequent evidence suggested that isoflurane anesthesia *per se*, rather than mechanical ventilation during anesthesia, was associated with the change in volume kinetics (Fig. 3) (8).

Surgical trauma appears to result in acute sequestration of IF. In otherwise healthy patients who received sodium-free fluid during open upper abdominal surgery, ECV decreased nearly 2 L and glomerular filtration rate (GFR) declined acutely by 13%. In contrast, patients who received LRS maintained ECV and

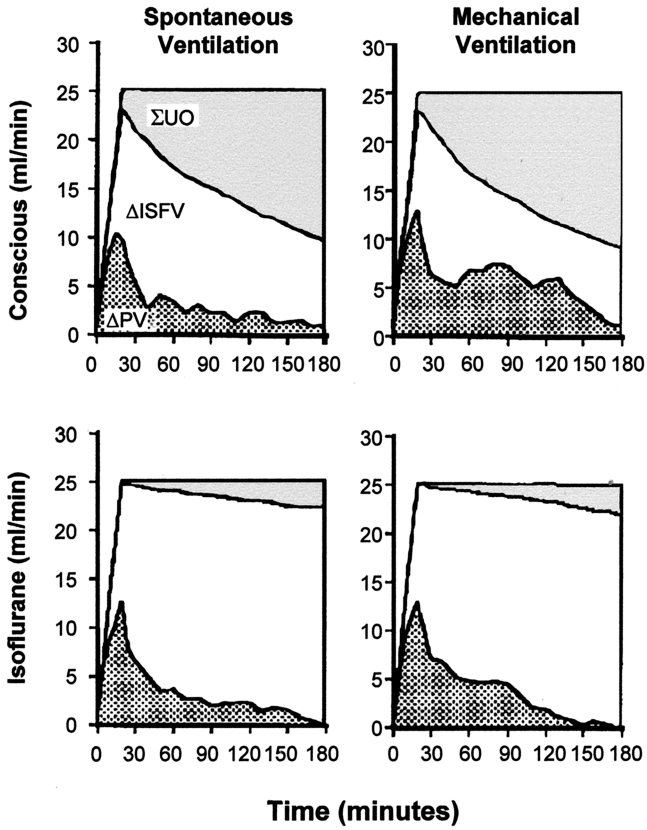

Figure 3. Indicator dilution and mass balance calculations during the four experimental protocols plotted as area graphs: ΔPV = net change in plasma volume (bottom light shaded area); ΔISFV = net change in interstitial fluid volume (middle white area); ΣUO = cumulative urinary output (upper dark area). Protocols studied are as follows: conscious, spontaneously ventilating group; conscious, mechanically ventilated group; isoflurane-anesthetized, spontaneously ventilating group; isoflurane-anesthetized, mechanically ventilated group. From Connolly et al. (8) with permission of the publisher.

increased GFR by 10% (9). During the first 10 days after resuscitation from multisystem trauma, patients demonstrated an increase in total body weight and a 55% increase in IFV (more than 5.0 L in a 70-kg patient) (10). Accumulated fluid mobilizes and returns to the PV, most commonly on the third postoperative day. If the cardiovascular and renal systems are unable to compensate, hypervolemia and pulmonary edema may occur.

The lack of a simple, objective method of defining and achieving adequate fluid resuscitation represents an ongoing deficiency in perioperative fluid management. Potential end-points for fluid resuscitation include measurements of the adequacy of preload, such as central venous pressure (CVP), pulmonary arterial occlusion pressure, corrected flow time (measured using an esophageal Doppler monitor) and gastric intramucosal pH (pHi, measured using a gastric tonometer). Venn et al. (11) reported that repeated colloid fluid boluses, given either until an additional bolus caused an increase ≥3 mm Hg in CVP or failed to increase stroke volume despite a corrected flow time ≥0.4 s, were associated with shorter time to discharge from the hospital than conventional fluid management in patients undergoing repair of hip fractures. In patients undergoing major elective surgery, use of fluid challenges to achieve a target corrected flow time of 0.40 s was associated with earlier return of bowel function, lower incidence of postoperative nausea and vomiting, and decreased length of hospital stay (12).

A recent review by Groeneveld and Kolman (13) provides a comprehensive review of the physiology, methodology, and physiologic aspects of gastrointestinal tonometry. Trinder et al. (14) found that a sustained low pHi (pHi <7.32 for >1 h) was associated with mortality but that a decreased pHi often developed many days before death. Moreover, although low pHi was an early prognostic indicator of mortality, it was not specific; the majority (70%) of patients with a low, sustained pHi recovered with conventional therapy. The prognostic value of monitoring pHi improved when used in combination with serial determinations of blood lactate (15).

Another potential definition of adequate fluid resuscitation is that which achieves a target level of systemic oxygen delivery (Do_2). In a single term, Do_2 combines cardiac output (Q) and arterial oxygen content (CaO_2), according to the equation:

$$Do_2 = Q \times CaO_2 \times 10$$

where the factor 10 corrects CaO_2 from mL O_2/dL to mL O_2/L.

In high-risk surgical patients who survived, average Q and Do_2 were greater than in those who succumbed to critical illness (16). Survival was strongly associated with a Do_2 ≥600 mL $O_2 \cdot min^{-1} \cdot m^{-2}$ (16) (equivalent to a cardiac index of 3.0 L $\cdot$ $min^{-1} \cdot m^{-2}$, a Hb concentration of 14 g/dL, and 98% oxyhemoglobin saturation). In attempting to increase Do_2, several principles should be kept in mind. First, the use of crystalloid or colloid fluids to increase Q will also decrease Hb concentration; therefore, the net effect on Do_2 will depend on whether the increase in Q or the decrease in Hb concentration predominates. Second, primarily increasing Hb concentration with blood transfusion (which increases blood viscosity) will often result in a reciprocal decrease in Q; again the net effect must be measured. Third, infusion of catecholamines, often necessary to achieve targeted Do_2 end-points, exerts drug-dependent effects on tissue perfusion and may have different effects on outcome. Fourth, other end-points, such as lactate or gut intramucosal pH (pH_i), might ultimately prove to be superior to nonselectively increasing Do_2 although evidence is inconclusive at this time.

Several recent trials illustrate the difficulties in resolving the question of whether targeted hemodynamic perioperative management improves outcome. Bishop et al. (17) advocated $Do_2 \geq 600$ mL $O_2 \cdot m^{-2} \cdot min^{-1}$ for resuscitation of trauma patients based on data suggesting better outcome. However, Velmahos et al., (18) in a later study of trauma patients at the same institution, found that trauma patients randomized to receive either conventional management or maintenance of $Do_2 \geq 600$ mL $O_2 \cdot m^{-2} \cdot min^{-1}$ did not differ in outcome, although patients in the conventional management group who spontaneously achieved $Do_2 \geq 600$ mL $O_2 \cdot m^{-2} \cdot min^{-1}$ and patients in the treatment group who therapeutically achieved that level had a much better outcome than patients from either group who failed to achieve that end-point. Patients in the treatment group who failed to achieve the end-point had a particularly poor outcome, perhaps suggesting some adverse effect of aggressive hemodynamic therapy in vulnerable patients.

Some clinicians are concerned that interventions used to increase Do_2 to specific targets may be detrimental (19). Tachycardia, a known side effect of several inotropic agents, may increase the risk of myocardial ischemia, although Yu et al. (20) found no increased risk of myocardial infarction during augmentation of oxygen delivery for critically ill patients. Another concern is that therapeutic interventions may disrupt individual organ function. For example, attempts to increase systemic oxygen transport with dobutamine, but not dopexamine, induced alterations in hepatic ultrastructure (21).

Of particular importance is the observation that the choice of catecholamine used to augment cardiac output may influence outcome. Wilson et al. (22) found that preoperative optimization, including inotropic support with dopexamine, was associated with fewer complications and shorter hospital stays in high-risk surgical patients than conventional treatment (control patients) or inotropic support using epinephrine, although both drugs significantly reduced the mortality rate in comparison with control patients. Subsequently, analysis of cost data from that study suggested that preoperative optimization was associated with a statistically significant reduction in hospital costs (23). However, neither of two fixed doses of dopexamine lowered mortality in a randomized study of patients undergoing major abdominal surgery (24). Although dobutamine appeared to slightly worsen outcome in a randomized trial in a mixed population of critically ill patients (19), a recent randomized trial comparing conventional management to augmentation of Do_2 using volume expansion and dobutamine in patients older than 60 yr reported better outcome in the treatment group (25). Most recently, Sandham et al. (26) reported that support of Do_2 using fluid loading (fluid type not specified by the protocol), inotropic

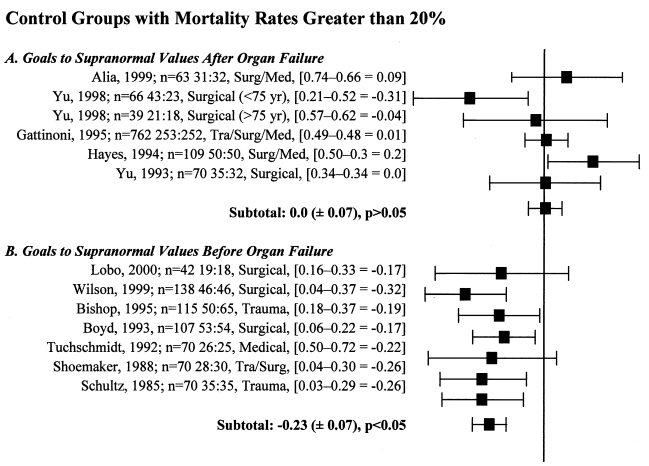

Figure 4. Mortality differences between protocol and control groups with control group mortality of >20%. Therapeutic goals are specified as supranormal or normal hemodynamic values. Data for each analyzed study include the first author's last name, date of publication, number of randomized subjects, number of subjects evaluated in treatment vs control groups, type of population (surgery, medical, or trauma), mortality of treatment patients minus control mortality, and the difference between treatment and control mortalities. From Kern et al. (27) with permission of the publisher.

therapy (drug not specified by the protocol), vasodilator therapy, vasopressor therapy for hypotension, and blood transfusion for a hematocrit <27% was not associated with improved outcome in patients undergoing high-risk surgery. However, failure to specify either the type of fluid given or the inotropic support is a weakness of this study.

A recent meta-analysis of hemodynamic optimization in high-risk patients that did not include the study by Sandham et al. (26) concluded that optimization revealed statistically significant reductions in mortality when optimization was begun early, before development of organ failure, when control group mortality exceeded 20% and when therapy produced differences in Do_2 between control and protocol groups (Fig. 4) (27).

Although much of the research regarding perioperative fluid management is directed at ensuring adequate resuscitation, an equally important problem is excessive perioperative fluid infusion. Arieff (28) reported 13 episodes of fatal postoperative pulmonary edema, apparently related to administration of large volumes of intra- and postoperative fluid. He also estimated, based on a 1-yr retrospective review of patients undergoing major surgery at two university medical centers, an annual incidence of 8,000 to 74,000 cases of postoperative pulmonary edema in the United States (28). Most troubling was the observation that 2.6% of patients without important comorbidities developed pulmonary edema and, of these patients, 3.9% died (28).

Another troubling aspect of current fluid management is that both the choice of fluids and the rapidity

with which fluid is administered may influence immune function. In rats subjected to hemorrhage and resuscitation with lactated Ringer's solution, hypertonic saline, or whole blood, resuscitation with lactated Ringer's solution increased immediate cell death by apoptosis in both the small intestine and liver, in contrast to those treated with hypertonic saline or whole blood or even those that were unresuscitated (29). In a similar model, resuscitation with plasma resulted in less lung apoptosis than resuscitation with lactated Ringer's solution or 6.0% HES (30). In mice subjected to surgical trauma and shock, slower fluid resuscitation (longer than 120 min) was associated with more rapid restoration of normal immune function than resuscitation over 30 or 60 min (31).

Colloid Development

The peak of controversy between advocates of crystalloid and those of colloid occurred more than 20 yr ago, then gradually subsided. The controversy was rekindled several years ago by two systematic reviews by the Cochrane collaboration of published, randomized trials (32,33). Both colloid in general (32) and albumin analyzed independently (33) were associated with an apparent increase in mortality. The pooled relative risk of death was greater in hypovolemic, burned, and hypoalbuminemic patients who received albumin, averaging 1.68 with confidence intervals of 1.26 to 2.23 (33). However, both reviews were extensively criticized, in large part because most of the trials on which the systematic reviews were based had been conducted many years previously. Interestingly, several of the recent reports that suggest that goal-directed fluid therapy improves various measures of outcome have used colloid to include filling pressure or corrected flow time (11,12).

The basic arguments in favor of crystalloid and colloid fluids have changed little in the past 20 yr. Arguments in favor of crystalloids emphasize lower cost, efficacy (if enough is given), better preservation of renal function, and rapid redistribution out of the vascular tree if overinfusion occurs. Arguments against crystalloids emphasize the large volumes necessary to achieve adequate intravascular expansion, the potentially adverse effects of diffuse soft tissue edema, and the potential for precipitating pulmonary edema by diluting serum proteins. Arguments in favor of colloid fluids emphasize greater efficacy in terms of expanding intravascular volume for any given volume of infused fluid and more prolonged retention within the vascular tree. In healthy male volunteers randomized to receive either 1000 mL lactated Ringer's solution or 6.0% HES over 5 min after withdrawal of 900 mL of blood, peak expansion of intravascular volume with lactated Ringer's solution, even immediately after infusion, was only 630 ± 127 mL, in contrast to 5 min after infusion of HES, at which point peak expansion was 1123 ± 116 mL (34). Arguments against colloids emphasize lower glomerular filtration rate with colloid resuscitation, interference with coagulation (especially with higher doses of hydroxyethyl starch and dextran) and more prolonged hydrostatic pulmonary edema if overinfusion occurs. Perhaps the most convincing arguments are the more prolonged expansion of intravascular volume accompanying colloid infusion in situations of major fluid loss, such as extensive surgery, and the lower cost of crystalloid fluids for most routine situations.

Regardless of the controversy, development of newer colloid fluids continues, often emphasizing alterations in the composition or diluent of HES formulations. HES solutions are characterized by three numerical factors: average molecular weight, degree of substitution, and substitution site. For example, an HES solution designated 200,000/0.5/4.6 would have an average molecular weight of 200,000 (although the mixture will contain a variety of sizes of molecules), a substitution ratio of 0.5 (half of the anhydroglucose sites will have hydroxyethyl groups), and substitution at 4.6 times as many C_2 as C_6 sites.

Potentially important clinical differences associated with differing constituents of HES solutions include changes in coagulation. Multiple recent studies have suggested that HES administration is associated with increased blood loss in cardiac surgical patients (35,36). The usual clinical response to hemodilution with saline is induction of a slightly hypercoagulable state (37). In experimental animals, hemodilution with albumin, but not Hextend®, an HES solution dissolved in a balanced electrolyte solution including lactate, also caused hypercoagulability (38). In patients randomized to receive lactated Ringer's solution, Hextend®, or HES 130,000/0.4, blood loss was greatest in the Hextend® group and did not differ between the other two fluids (39). In contrast, Gan et al. (40) reported slightly lower blood loss and use of blood products in patients receiving Hextend® than in those receiving HES dissolved in saline.

The choice of diluents also may exert clinically important effects. The HES solution commonly used in the United States is dissolved in 0.9% saline and, when infused in large doses, is associated with hyperchloremic metabolic acidosis. Hextend®, an HES solution dissolved in a balanced electrolyte solution including lactate, should be less prone to this complication and may exert less effect on coagulation, perhaps because of the inclusion of a modest amount of calcium in the diluent (40). As would be predicted, perioperative administration of balanced salt solutions and Hextend® was associated with less hyperchloremic acidosis than administration of saline and HES dissolved in saline (41). It is interesting that the composition of

HES solutions should now be receiving so much attention, given the long and generally safe record of earlier formulations. Further research is necessary to define the clinical value and cost-effectiveness of the newer products.

Specific Components of Intravenous Crystalloid Fluids

Crystalloid fluids have many components that vary among specific formulations, but three components (sodium, lactate, and chloride) have received considerable attention recently. The importance of sodium concentration is based on the effects of changing serum osmolality on brain water as well as a variety of other effects of hypertonic resuscitation fluids. Lactate, originally added to lactated Ringer's solution as a precursor for bicarbonate, now appears to exert pharmacologic effects that may be disadvantageous. Chloride, in the higher than physiologic concentrations present in 0.9% saline, has now been associated clearly with hyperchloremic metabolic acidosis that is dose-dependent.

Because the normal blood-brain barrier is highly impermeable to sodium, small changes in serum sodium exert greater osmotic pressure gradients across the cerebral capillary bed than do relatively large changes in serum protein concentrations (42). For instance, an increase of 5 mEq/L in serum sodium would increase osmolality by 10 mOsm/kg, or 186 mm Hg of osmotic pressure. In contrast, the osmotic pressure exerted by a normal serum protein concentration across the blood-brain barrier would be only approximately 23 mm Hg (Table 2).

The effects of changes in colloid osmotic pressure and serum sodium on brain water or intracranial pressure (ICP) have been extensively studied in animals with normal brains, in experimental models of brain injury, and in humans. In anesthetized rabbits, plasmapheresis that reduced plasma [Na^+] sufficiently to reduce plasma osmolality by 13 mOsm/kg (baseline value = 295 mOsm/kg) increased cortical water content and ICP. In contrast, reducing protein to reduce oncotic pressure from 20 to 7 mm Hg produced no change in either variable (42). Reduced colloid osmotic pressure also did not increase brain water after experimental cryogenic injury (43). Because the blood-brain barrier enhances the influence on brain water of changes in serum sodium (42), hypotonic solutions (including lactated Ringer's solution) are more likely to increase brain water content than 0.9% saline or colloids dissolved in 0.9% saline. However, after traumatic brain injury (TBI), Drummond et al. (44) demonstrated that colloid osmotic pressure could influence brain water accumulation, perhaps because TBI, especially if accompanied by secondary hypoxic injury, damages the blood-brain barrier (45).

Hypertonic sodium solutions acutely reduce brain water and therefore tend to reduce ICP. In a double-blind, cross-over study in head-injured children, 3.0% saline decreased ICP significantly, whereas 0.9% saline had no effect (46). It is reasonable to speculate that the effects on ICP represent a combination of interstitial and cellular dehydration. In animals with cryogenic brain injury, hypertonic solutions reduced ICP and decreased brain water in normal brain tissue (47). In animals with intracranial mass lesions and hemorrhagic shock, resuscitation with hypertonic saline also improved regional CBF and cerebral oxygen delivery (48). Other experimental data also suggest the possibility of rebound intracranial hypertension after hypertonic resuscitation from shock and intracranial hypertension (49).

It is important to consider the comparability of experimental models to the clinical situation. Models that examine the acute effects of rapid administration of fluids of varying tonicity usually demonstrate differences in brain water; those that look at slower, "maintenance" rates of administration usually find negligible differences. Shapira et al. (50) compared the effects on brain water of a variety of fluids administered to head-injured rats for 18 h after injury. No differences in brain edema were evident among groups that were fluid restricted and those infused with 25% glucose, 5% dextrose in 0.45% saline, or an isotonic gelatin-based plasma expander.

Clinical trials have evaluated hypertonic solutions for prehospital resuscitation. Vassar et al. (51) compared 250 mL of LRS with 7.5% saline in 6.0% dextran 70 for prehospital resuscitation of trauma patients in whom systolic blood pressure was $\leq$100 mm Hg. Although there was no overall difference in mortality, in the subset of patients with severe head injury (53 of 186 patients), 32% of those who received HSD survived, versus only 16% of the patients who received LRS ($P = 0.04$). In a subsequent randomized multicenter study, Vassar et al. (Table 3) evaluated the effects of 250 mL of sodium chloride with and without 6% and 12% dextran 70 for the prehospital resuscitation of hypotensive trauma patients (52). A small subgroup of patients with Glasgow Coma Scale scores <8 but without severe anatomic injury seemed to benefit most from resuscitation with 7.5% saline (52).

Less hypertonic solutions have been used for in-hospital resuscitation of patients with head injury. Shackford et al. (53) used hypertonic lactated saline (Na concentration 250 mEq/L) or LRS to treat systolic blood pressures $<$90 mm Hg or urinary output $< 0.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ during the first 5 days of intensive care. Although the hypertonic group required more interventions to reduce ICP, the baseline ICP was higher in that group and the overall trend in

Table 2. Acute Effects of Changing Osmotic Pressure in the Cerebral Capillaries

	Osmolality (mOsm/kg)		Osmotic Pressure (mm Hg)		Osmotic Pressure Difference (mm Hg)
	Plasma	IF	Plasma	IF	(Plasma − IF)
[Na^+], protein, nonprotein	282.6	282.6	5454	5454	0
[Na^+] acutely ↑ 5.0 mEq/L	292.6	282.6	5640	5454	186
Protein	1.2	0	23	0	23
Protein ↑ × 2	2.4	0	46	0	46

IF, interstitial fluid.

Table 3. Predicted Versus Actual Survival

	LR	HS	HSD-6%	HSD-12%
Entire cohort (*n*)	45	50	50	49
Predicted (%)	47	48	52	40
Actual (%)	49	60	56	45
GCS ≤ 8 (*n*)	25	29	26	30
Predicted (%)	14	13	16	14
Actual (%)	12	34	27	30

Trauma patients with hemorrhagic shock; randomized to immediate resuscitation with 250 mL of lactated Ringer's solution (LR) or 250 mL of 7.5% saline (HS) 7.5% saline with 6% dextran 70 (HSD-6%), or 7.5% saline with 12% dextran 70 (HSD-12%). Predicted survival from TRISS scores.
Modified from (52) with permission of the publisher.
GCS = Glasgow Coma Scale score.

ICP was more favorable. Simma et al. (54) randomized severely head-injured children to receive either hypertonic saline (Na concentration 268 mEq/L) or LRS for the first 3 days after injury. The children receiving hypertonic saline required fewer interventions to maintain ICP <15 mm Hg and had fewer overall complications, although survival and duration of hospital stay were similar. Other investigators also have reported extensive experience with the use of hypertonic saline solutions for maintenance therapy in neurologic patients (54–56).

Other effects of hypertonicity also have received increasing attention. Among reported physiologic changes associated with hypertonic fluids include alterations in the cytotoxicity of polymorphonuclear leukocytes (57), sequestration of neutrophils in the lung (58), priming of neutrophils (59), and endotoxin-induced vascular permeability (60). Initial concerns regarding the adverse neurologic sequelae of hypertonic resuscitation appear to have been premature. Patients tolerate acute increases in serum sodium to 155–160 mEq/L without apparent harm (51,61). Third, central pontine myelinolysis, which occasionally follows rapid correction of severe hyponatremia, appears to be most likely after correction of chronic hyponatremia (62) and has not been observed in clinical trials of hypertonic resuscitation.

Lactate, long considered to have no pharmacologic effects other than serving as substrate for production of bicarbonate, appears to exert important effects on cellular function, at least in experimental animals. In rats resuscitated from hemorrhagic shock, lactate infusion is associated with increased apoptosis in both the gastrointestinal tract and liver (29). Also in rats, LRS was associated with rate-dependent immune suppression (31). However, LRS improved survival in comparison to 0.9% saline in rats with massive hemorrhage (63). Clearly, further work is necessary to define appropriate constituents and rates of delivery of various crystalloid fluids.

Perhaps one of the more surprising sets of observations regarding fluid therapy in the last decade has been the recognition that 0.9% saline, long a mainstay of fluid management, produces dose-dependent hyperchloremic metabolic acidosis. Taken as a group, several recent articles (64–66) suggest that metabolic acidosis is a direct consequence of rapid replacement or expansion of extracellular volume with fluid containing no bicarbonate (67,68). If the fluid contains bicarbonate substrate (e.g., lactate), the acidosis is more quickly resolved than if the fluid contains chloride in concentrations that exceed normal (5).

Summary

Fluid management has progressed rapidly in the last three decades. Current regimens are sufficient to restore systemic perfusion in the majority of patients undergoing surgery. However, important questions remain to be answered regarding the frequency of complications of current fluid therapy and the comparative advantages of different fluid formulations in a variety of clinical circumstances.

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