INTRODUCTION

Fluid management is an essential part of patient care in the perioperative period. Adequate plasma volume is vital in maintaining cardiac output and hence tissue perfusion. Inadequate tissue perfusion is associated with poor outcome following surgery. Fluid management strategies have undergone several shifts over the past fifty years. Prior to the sixties, fluid restriction during the intraoperative period was widely practiced. In the early 1960s, it was demonstrated that major surgery and trauma were associated with fluid requirements that significantly exceeded the usual rate of fluid maintenance. As a result, fluid administration became less restrictive. A decade later, the choice of fluid became the subject of intense debate, and continued till today, as colloid versus crystalloid controversies are still raging on. In the late eighties and early nineties, the concept of achieving a “supranormal” oxygen delivery attracted much interest. More recently, goal-directed fluid management appears to show benefits in surgical settings. The last few years saw the development of new colloid solution, with its physical characteristics and its “balanced electrolyte” carrier.

FLUID COMPARTMENTS

Accurate replacement of fluid deficits requires an understanding of the distribution volume of body fluids. For a person weighing 70 kg, total body water (TBW) is about 42 L. The total body water exists within discrete but dynamic fluid compartments. Two thirds of the TBW (28 liters) is intracellular water. The remaining third (14 liters) in the extracellular compartment is divided into the intravascular (5L) and extravascular (9L) compartments. Blood is composed of around 60% plasma (extracellular compartment) and 40% red and white blood cells and platelets (intracellular compartment). Plasma consists of inorganic ions (predominantly sodium chloride), simple molecules such as urea and larger organic molecules (predominantly albumin and the globulins) dissolved in water. Interstitial fluid bathes the cells and allows metabolic substrates and wastes to be diffused between the capillaries and cells in the tissue. Excess free interstitial fluid enters the lymphatic channels and is ultimately returned to the plasma. The majority of the interstitial water exists within a proteoglycan matrix in a gel form. The “transcellular fluids” are extracellular and extravascular and include the cerebrospinal fluid, acqueous humor, pleural, pericardial, peritoneal and synovial fluids.

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) compartment. Water moves freely through cell and vessel walls and distributes throughout all these compartments. The energy dependant Na+/K+ ATPase in cell walls excludes Na+ and Cl- ions 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 Na+ and Cl-, but is relatively impermeable to larger molecules such as albumin and the semi-synthetic colloids e.g. gelatins and starches which are maintained in the intravascular space. The protein and synthetic colloids therefore exert a colloid oncotic pressure (COP) which serves to retain plasma water within the intravascular compartment.

Colloid Oncotic Pressure and Fluid Flux

Colloid Oncotic Pressure (COP) is the osmotic pressure exerted by the macromolecules (the colloid molecules). Solutes that can pass freely across a semi-permeable membrane do not generate any oncotic pressure - they are effectively a component of the solvent with respect to that membrane. Where membranes are selectively permeable to solutes the water content of the fluid compartments is dictated by solute distribution as water moves down any osmotic pressure gradient to produce isotonicity. The COP of the plasma is only one of several forces determining fluid flux at the vascular membrane. Starling in 1896 first described the forces affecting the flux of fluid across the capillary membrane. These forces can be expressed in the following equation:

\[ Q_V = K[(P_C - P_T) - \sigma_C(\pi_C - \pi_T)] \]

in which \( Q_V \) = total flow of fluid across the capillary membrane; \( K \) = fluid filtration coefficient; \( P_C \) = capillary hydrostatic pressure; \( P_T \) = interstitial hydrostatic pressure; \( \sigma_C \) = reflection coefficient; \( \pi_C \) = capillary COP (plasma); \( \pi_T \) = interstitial COP. The filtration coefficient is a function of the permeability and surface area of the capillary bed in question. The numeric value represents the net volume of fluid crossing the capillary membrane under a specific set of conditions. The reflection coefficient is a mathematical expression (from 0 to 1) of the capillary membrane’s permeability to a particular substance. Thus the reflection coefficient will vary with both the tissue bed and substance in question. If a substance is completely impermeable to the capillary membrane, the reflection coefficient will be 0; if it is totally permeable, the coefficient will be 1.
For protein, the approximate reflection coefficients for liver, lung, and brain are 0.1, 0.7, and 0.99, respectively. When a pulmonary insult creates a leaky capillary state, the protein-lung reflection coefficient may decrease to approximately 0.4. The reflection coefficient for albumin, the source of 60% of the normal oncotic pressure in the pulmonary circulation, is approximately 0.7.

The composition of administered fluids will therefore dictate their distribution. Pure water expands all body fluid compartments and therefore provides minimal expansion of the intravascular volume. Intravenous infusion of an isotonic solution of sodium chloride expands only the extracellular compartment and will increase intravascular volume by about one fifth of the volume infused. Colloidal solutions containing large molecules are maintained within the circulation, at least initially, and so provide greater intravascular volume expansion per unit volume infused. Lamke and Liljedahl demonstrated that 90 minutes following infusion of 1000 mL of 6% hetastarch, albumin or saline in postoperative surgical patients, 75% and 50% of the hetastarch and albumin respectively, still remain in the intravascular space, whereas only less than 20% of saline remained.

**CHOICE OF FLUIDS**

The choice of intravenous fluids may broadly be categorized as colloids and crystalloids. Crystalloids are effective and appropriate for the initial management of extracellular compartment losses associated with hemorrhagic shock, major surgery or trauma. After this acute resuscitation phase, there usually is a significant degree of hemodilution and a diminished plasma COP. This reduction in plasma COP has been associated with the development of edema and transudates. It is therefore appropriate that continued fluid resuscitation should include colloid solutions in an attempt to minimize interstitial edema within vital organs e.g. heart, lung and brain. Colloids are defined as having larger molecular weight and hence would remain in the vascular space for a longer period of time. Colloid-containing resuscitation protocols have been demonstrated to have the ability to either maintain or increase the plasma COP. Colloids available in the US include synthetic starches, albumin and dextran.

**Hydroxyethyl Starch**

The hydroxyethyl starch (HES) compounds are a group of polydisperse synthetic colloids that resemble glycogen structurally. Hetastarch is a high molecular weight HES, with an average molecular weight of 450,000 d with 80% of the polymers falling in the range of 30,000 d to 2,500,000 d. However, for polydisperse colloids, the number-average molecular weight (MWN) provides a better representation of the number of particles of a given size as opposed to the weight-average molecular weight. Hydroxyethyl starches are synthesized from amylopectin, a waxy starch derived from maize or sorghum. Amylopectin is a D-glucose polymer with a branching structure. Reaction with ethylene oxide in the presence of an alkaline catalyst results in hydroxyethyl substitution. The majority of these substitutions occur at carbon 2 in the glucose ring with the rest occurring at carbon 3 and 6. Increased C2/C6 substitution ratio results in slower enzymatic degradation. The unsubstituted starch is rapidly hydrolyzed by non-specific α-amylases in the plasma and substitution with hydroxyethyl groups substantially slows this process. The degree of substitution (DS) indicates the proportion of glucose moieties that have been substituted and is expressed as a number from 0-1. Starches with a DS close to 1 have a greater resistant to hydrolysis than those with a lower DS. The substituted starch is then refined into the final product by hydrolysis to the required molecular weight, purification and for certain products a fractionation process to produce specified molecular weight bands. Hetastarch is primarily excreted via the kidneys. Particles weighing less than 50,000 d are rapidly filtered through the kidneys with 40% -50% of the administered dose eliminated within 48 hours.

Pentastarch is a smaller molecular weight molecule with an average molecular weight of about 200,000. It has a shorter half-life and does not seem to affect the reticulo-endothelial system. Pentastarch 10% has a good initial volume-expanding capacity of 1.2 times the infused volume. About 90% is eliminated within 24 hours and most is undetectable after 96 hours. Recently, Voluven, a third generation low molecular weight hetastarch (140kD/0.4) was approved in the USA.

**Albumin**

Albumin is a naturally occurring plasma protein composed of 584 amino acid residues. The molecular weight of albumin ranges from 66,000 to 69,000 depending on the technique of measurement. The molecule is highly soluble and carries a strong negative charge at physiological pH. Consequently, albumin migrates in the electrical fields. Depending on the salt and buffer concentration of the plasma, albumin is isoelectric in the pH range of 4.4 and 5.4. In serum, albumin is in part bound to either cations or anions. This property accounts for its role as a carrier protein for the transport and activation of drugs, hormones, enzymes, fatty acids, amino acids, bilirubin and other metabolites. The half-life of circulating albumin is approximately 18 to 20 days. Albumin provides approximately 70% of the plasma colloid oncotic pressure in normal human subjects. Human albumin is available for infusions as either 5% or 25% solution. The 5% solution is approximately iso-oncotic with that of normal subjects, whereas the 25% solution is markedly hyperoncotic. Human albumin is prepared from human plasma following a heating process for 10 h at 60°C.

Plasma protein fraction (PPF) is a 5% solution of selected proteins prepared from pooled human blood, serum, or plasma. It undergoes the same pasteurization process used for albumin and is a mixture of proteins consisting mostly of albumin in an amount equal to
or greater than 83% of the total protein composition. Although albumin solution may be more purified and contains a greater percentage of albumin (>93%), the two solutions are similar in costs, and hence are used interchangeably.

Dextran

Dextran are high molecular weight D-glucose polymers linked by alpha1,6 bonds into predominantly linear macromolecules. They are biosynthesized commercially from sucrose by the B512 strain of Leuconostoc mesenteroides using the enzyme dextran sucrase. This produces a high molecular weight dextran that is then cleaved by acid hydrolysis and separated by repeated ethanol fractionation to produce a final product with a relatively narrow molecular weight range. The products in current clinical use are described by their MWN: Dextran 40 and Dextran 70 having MWNs of 40,000 and 70,000 dalton respectively.12

Infusions of hyperosmotic-hyperoncotic solutions such as hypertonic saline dextran has been shown to be very effective in expanding plasma volume rapidly. The intravascular volume expansion efficiency, defined as milliliter plasma expansion/milliliter fluid infused was 7 and 20 folds at 30 and 60 min after infusion, respectively when hypertonic saline dextran was compared with lactated Ringer’s solution (LR).13

**SALINE VS. “BALANCED” ELECTROLYTES BASED FLUIDS**

Colloids and crystalloids may be divided into whether they are formulated in 0.9% sodium chloride or a variety of balanced electrolytes solutions. Lactated Ringer’s and Normosol solutions consist of a number of electrolytes that are present in the plasma, whereas 0.9% saline is made up of only sodium and chloride. There appears to be differences between saline vs. balanced electrolyte based solutions when used clinically.

**Acid Base balance and renal outcome**

In a human volunteer crossed-over study, Williams and colleagues found a significantly higher incidence of subjective mental changes, abdominal discomfort, as well as a significant delay of time to first urination, in the group that received 50 mL/kg of 0.9% sodium chloride over 1 hr compared with the same volume of lactated Ringer’s solution, along with a transient decrease in blood pH. Schein graber et al. demonstrated a significant hyperchloremic acidosis at the end of surgery in patients undergoing major gynecological hysterectomies when 0.9% sodium chloride was used as the intraoperative resuscitative fluid.15 In a recent study of geriatric surgical population undergoing major non-cardiac surgery, the perioperative use of balanced electrolyte solutions (Hartmann’s solution and Hextend) was associated with significantly lower incidence of hyperchloremic metabolic acidosis (0% versus 66%) in saline group and better gastrointestinal mucosa perfusion compared with sodium chloride based solutions (0.9% saline and Hespan). Other studies have demonstrated the predictability of acidosis following intraoperative administration of saline based fluid.16-19

**HEMOSTATIC EFFECTS OF COLLOIDS**

The choices of fluid administered intraoperatively can result in differences in the coagulation effects. Hespan in larger volume (>20 mL/kg) has been associated with reduced levels of the coagulation factors, e.g., fibrinogen, Factor VIII, and von Willebrand’s factor and reduced platelet function, beyond the effect of hemodilution. This has prompted the FDA to issue a warning against high volume administration in its package insert. Crystalloid administration, however, is associated with a hypercoagulative state.20

A recent study demonstrated a better thromboelastographic (TEG) coagulation profile when larger volumes of Hextend® (>20 mL/kg) was used compared with equivalent volumes of 6% hetastarch in saline (Hespan).21 Hespan was associated with a hypocoagulable state with prolongation of both their r time and k time and a reduction in MA on thromboelastography. This hypocoagulable state continued into the first 24 hours postoperatively.22 LR solution, however, was associated with a hypercoagulable state.23,24 The TEG profiles with respect to Hextend® showed the least change.22 When used for acute normovolemic hemodilution, hetastarch and dextran appeared to attenuate the hypercoagulative state seen when LR and albumin were used.24 In another study when Hextend was compared with albumin, there appeared to be no differences in the levels of Factor VIII, von Willebrands factors and platelets up to 24 hours following major surgery.25 Boldt et al. compared a high molecular weight hydroxyethyl starch (Hextend), a low molecular weight hydroxyethyl starch (130kDa, DS=0.4) and lactated Ringer’s in patients undergoing major abdominal surgery. The patients in the Hextend group experienced more blood loss, and needed more blood and blood products, compared with the other two groups. Interestingly, the standard coagulation tests (PT, APTT and platelets) showed no significant differences between the groups up to 2 days following surgery.26

**GOAL DIRECTED FLUID ADMINISTRATION**

Since the late 1950’s a succession of authors have described an association between perioperative cardiac output and survival following major surgery: the survivors exhibiting higher values than the non-survivors. From these observations the hypothesis developed that using the cardiac output and oxygen delivery values exhibited by the survivors, as goals for all patients would reduce overall mortality. Shoemaker et al. demonstrated that targeting specific values for cardiac index, oxygen delivery and oxygen consumption, using fluids and inotropes to achieve these goals, resulted in a reduction in mortality and morbidity.
Since then a number of single center randomized controlled trials have been conducted, the majority of which support this original positive result. Five studies have used the same hemodynamic goals as the original study by Shoemaker. Two of these were large (>100 patient) studies on high-risk general surgical and vascular patients and both demonstrated a statistically significant reduction in mortality in the protocol groups. Two were studies of major trauma surgery and these were both conducted by the same group. The first smaller study showed a trend towards reduction in mortality in the protocol group and this was confirmed by a statistically significant reduction in protocol group mortality in the second, larger trial. The fifth study in this group was a small trial focusing on surgery for hepatobiliary carcinoma and demonstrated a reduction in liver failure and hyperbilirubinemia although this was not their specified primary outcome variable. An older study using a similar philosophy, but with less clearly defined goals, in patients undergoing hip fracture surgery also demonstrated a significant mortality reduction. Somewhat different results have been obtained in a series of papers in which patients presenting for major vascular or aortic surgery were studied. The goals for cardiac index and oxygen delivery used in these trials were significantly lower and the overall mortality for each trial was also low. These studies did not demonstrate a significant reduction in mortality, or in some cases complications, however in only one of these studies were there more deaths in the protocol than control groups.

Targeting mixed venous oxygen saturation (SvO2) as an indirect index of oxygen delivery has also been studied in two trials. The first studied patients having aortic or lower limb arterial surgery and failed to demonstrate a significant morbidity or mortality difference between control and protocol groups. More recently a large Scandinavian study of patients undergoing elective coronary revascularization with cardiopulmonary bypass demonstrated a significant reduction in length of stay in those randomized to maintenance of SvO2 > 70% and lactate ≤ 2 mmol/L when compared with controls.

A number of published studies using intraoperative esophageal Doppler monitoring of cardiac output compared a stroke volume optimization algorithm with standard fluid management. In the first study patients with normal left ventricular function undergoing coronary artery revascularization had a statistically significant reduction in length of stay in those randomized to maintenance of SvO2 > 70% and lactate ≤ 2 mmol/L when compared with controls. The second study, of elderly patients having hip prosthesis surgery, also demonstrated a reduction in hospital length of stay in patients managed in the protocol group. Gan and colleagues, in a recent study using a similar optimization algorithm demonstrated a reduction in hospital stay and earlier return to tolerating solid food in the protocol group undergoing major non-cardiac surgery. Conway et al also demonstrated a lower incidence of ICU admission in the goal-directed fluid therapy group.

The application of this management approach to patients with established critical illness has been much less successful. A number of single center studies and one large multi-center RCT have failed to show an outcome benefit for patients in the protocol group. Indeed in some studies the intervention group mortality exceeded that of the control group.

**COLLOID VS CRYSTALLOIDS**

Arguments over the best type of fluid for volume resuscitation have raged for more than 30 years. While all sides agree that fluid resuscitation is fundamental in the management of hypovolemia there is disagreement as to which solutions to use. Crystalloid supporters point to the hemostatic derangement, the increased incidence of adverse drug reaction and the greater risk of fluid overload occurring with colloidal fluids. The colloid lobby focuses on the large volumes of crystalloid required to achieve adequate resuscitation and on the resultant tissue edema and reduction in tissue oxygen delivery. A large number of RCTs have attempted to address this question in a number of clinical settings. There have been three meta-analyses focusing specifically on this issue with mortality as the endpoint. The most recent of these focused on 19 RCTs including 1315 patients and suggested an increase absolute risk of mortality of 4% with use of colloid for volume replacement (95% confidence interval 0% to 8%). However these meta-analyses have been widely criticized for pulling together a large number of studies comparing a number of different solutions amongst diverse patient populations, for varying indications. None of the original studies used mortality as a primary end point, the vast majority of studies included are of albumin or dextran solutions and these two colloids contribute all the excess mortality. At present there is a lack of adequate studies upon which to base a judgement on this question and many clinicians continue to use colloids in combination with crystalloids.

However, a recent study suggests that the quality of recovery may be superior when colloid/crystalloid combination was used compared with crystalloid alone in patients undergoing major non-cardiac surgery. Patients who received lactated Ringer’s alone had higher incidence of nausea and use of rescue antiemetic, double vision, and complained of more severe pain postoperatively.

**SUMMARY**

Perioperative fluid management has undergone significant advances over the past few decades. The choice of fluid and its electrolyte composition are important considerations when replenishing plasma volume and other body fluid compartments. The coming decade will likely see an expansion of knowledge defining the role of goal directed fluid therapy in clinical practice and the differences between colloids and crystalloids when used in the perioperative period.
REFERENCES