Intra-operative Fluid Management: Are there any new lessons?

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<u>Introduction</u>

Fluid management is an integral and important function for anesthesia providers during the perioperative period. Patients generally arrive with fluid deficits, have significant fluid shifts and have variable amounts of fluid loss during the perioperative period. These all lead to changes in intravascular volume, which ultimately impact perfusion and oxygen delivery. Thus appropriate fluid management is critical to the care of patients intraoperatively.

<u>Composition of Body Water</u>

Water comprises 60% of the total body weight (i.e., 600 ml/kg or 42 liters of a 70 kg patient is water). Total body water consists of the intracellular volume which comprises 40% or 400 ml/kg (±28 liters) plus the extracellular fluid volume (200 ml/kg or 14 liters). The extracellular volume consists of the interstitial volume (160 ml/kg or 11.2 liters) plus the plasma volume (30-40 ml/kg or 2.8 liters). The plasma volume constitutes 40-50% of the total blood volume (65 ml/kg). These various fluid volumes are separated by semipermeable membranes. The cell membrane separates the extracellular volume from the intracellular volume and the capillary membrane separate plasma volume from the interstitial volume. Water passes freely across these membranes and the net flow of fluid is determined by Starling's Law. In essence the equilibrium of fluid flow between such semipermeable membranes is determined by the effect of hydrostatic pressure and the osmotic pressure on either side of the semipermeable membrane. The osmotic pressure is dependent on the electrolyte composition of the various body fluids.

Table 1: Electrolyte composition of body fluids.

Electrolyte Composition of Body Fluids			
	Plasma (mEq/L)	**Intracellular Fluid (mEq/L)**	**Extracellular Fluid (mEq/L)**
Sodium	142	10	140
Potassium	4	150	4.5
Magnesium	2	40	2
Calcium	5	1	5
Chloride	103	103	117
Bicarbonate	25	7	28

<u>Fluid Loss</u>

Water is lost daily through urine (±1400 ml), sweating (±100 ml), feces (±100 ml), and insensible loss (±700 ml) for a total average daily loss of 2300ml. In addition to this daily fluid loss there are other losses during surgery. These include surgical blood loss as well as fluids lost through the opening of various body cavities. In addition as the primary goal is to maintain tissue perfusion, which is dependent on the intravascular volume, any losses from this compartment must also be compensated for. These losses include third space loss as well as fluid to compensate for intravascular volume expansion, secondary to venodilatory and cardiac depressant effects of anesthetics and other drugs used intraoperatively.

<u>Types of Fluids</u>

The types of fluids that are available for intravenous administration can be classified as either crystalloid or colloid. The crystalloids consist of balanced salt solutions, hypertonic solutions and dextrose. The colloids consist of synthetic colloids or starches, albumin and protein fractions, blood and blood products and most recently blood substitutes. The composition of the synthetic colloids and albumin is listed in Table 2 and for the commonly used balanced salt solutions is listed in Table 3. Blood substitutes have generated a lot of interest due to complications associated with red blood cell transfusion especially viral transfer. The primary objective for any blood substitute is to enhance intravenous oxygen carriage and its delivery to peripheral tissues. Numerous blood substitutes are presently under investigation but none have yet been approved for clinical use. These include recombinant hemoglobin, bovine stabilized hemoglobin, human stabilized hemoglobin and perfluorocarbons. The perfluorocarbons, which enhance oxygen carriage in plasma, are commercially available but have not been approved as blood substitutes. This review will not cover blood replacement therapy but rather concentrate on advances and controversies in intraoperative fluid administration with crystalloids and colloids.

Table 2 Composition of Synthetic Colloids and Albumin

Colloids								
Fluid	**Na mEq/L**	**K mEq/L**	**Cl mEq/L**	**COP**	**Osm**	**pH**	**MW**	**Other**
5% Albumin	145	< 2.5		35	330	7.4	69,000	
Hespan	154	0	154	30	310	5.9	69,000	
Hextend	145	3	124	30	310	6.5	69,000	Ca 5 mEq/L Mg 0.9 mEq/L
Dextran 70	0	0	0	40	255	4.0	70,000	
Pentastarch	154	0	154	40			120,000	

Table 3. Composition of Balanced Salt Solutions

Balanced Salt Solutions

Fluid	Na mEq/L	K mEq/L	Cl mEq/L	Dextrose g/L	Osm	pH	Other
Normal Saline	154	0	154	0	308	5.4	
Ringers Lactate	130	4	109	0	273	6.5	Lactate 28 mEq/L Ca 3 mEq/L
Normosol R	140	5	98	0	294	6.6	Mg 3 mEq/L acetate 27 mEq/L gluconate 23 mEq/L
Plasma-Lyte A	140	5	98	0		7.4	acetate 27 mEq/L gluconate 23 mEq/L
5% Dextrose	0	0	0	50	252	4.5	

As the net flow of fluid within the total body water is dependent on both hydrostatic and osmotic pressure the relative distribution of 1 liter of fluid will depend on its composition. As stated above we are primarily interested in the intravascular volume as this impacts cardiac output and thus tissue perfusion. One liter of water (with 5% dextrose which is osmotically inactive) will distribute throughout the total body water and result ultimately, once all fluids have equilibrated, in only a 14% expansion in plasma volume. A balanced salt solution will distribute itself within the extracellular fluid and will result in a 20-30% expansion in plasma volume once equilibration has occurred. This contrasts with the colloid solutions, which due to particles impermeable to the capillary membrane will result in a 60-100% expansion in plasma volume. Fluids that are not retained within the intravascular volume can ultimately lead to interstitial edema. Excessive interstitial edema can impair wound healing, reduce cardiac compliance, impair gas exchange within the lungs, reduce absorption and enhance bacterial translocation within the gut and in extremes obtund consciousness. This is especially true in the presence of reduced reserve, (e.g., increasing age or organ pathology). Not only is adequate resuscitation important but it is important to remember that interstitial edema also results in morbidity.

Choice of Fluids for Use Intraoperatively

Recently Bennett-Guerrero et al documented the outcomes in 438 patients following cardiac surgery. [Bennett-Guerrero, 1999 #3] Predictors of postoperative morbidity included age, ASA status, duration of surgery, blood loss and surrogates of hypovolemia and tissue hypoperfusion. Such data further emphasizes the importance of appropriate intraoperative fluid management. These complications were not limited to the initial postoperative period but rather were observed 5 to 15 days postoperatively.

The above arguments would tend to imply that we should abandon balanced salt solutions for colloids. The crystalloid/colloid debate has raged for many years. Recently there have been three important meta-analyses of the crystalloid/colloid/albumin debate. The Couchrane Injuries Group published in the *British Medical Journal* in 1998 their evaluation of the relative morbidity of administering crystalloid or albumin/protein plasma fraction for resuscitation secondary to hypovolemia. [, 1998 #4] Included in this analysis are 13 different studies consisting of 531 patients. These studies were included only if a mortality had been observed. Based on these studies they calculated the relative risk of death following the administration of colloid versus crystalloid. The relative risk for death was 1.46 (95% confidence interval, 0.97 to 2.22) when colloids were used for resuscitation either secondary to trauma or intraoperative blood loss. Choi et al in 1999 did a similar meta-analysis comparing crystalloid versus colloid for resuscitation in trauma and non-trauma patients. [, 1998 #4] In the trauma group there were five studies with 302 patients and in the non-trauma group 12 studies with 512 patients. Again taking death as the primary outcome variable they found no significant difference between the use of crystalloid versus colloid. They also looked at the incidence of pulmonary edema and length of stay and similarly found no difference based on the choice of fluid for resuscitation. Probably the most extensive meta-analysis was done by Wilkes and Navickis [Wilkes, 2001 #6] where they compared crystalloid versus albumin in 55 randomized trials, which included 3,504 patients. The trials included in this meta-analysis consisted of trauma, hyperalbuminemia, high-risk neonates, ascites, etc. They concluded the relative risk of death with albumin was 1.11 (95% confidence interval, 0.95-1.28). In a sub-group of this meta-analysis they determined that there was a reduced risk of death in patients receiving albumin, in those studies that were blinded, had mortality as an end point and that contained greater than 100 patients in the study.

All of these recent meta-analyses have been criticized for their selection bias of the studies included in the analysis. They also contain studies with very heterogeneous study designs and many of these studies did not have mortality as the original study endpoint. In many of these studies mortality was unrelated to fluid resuscitation and thus constitutes an inappropriate endpoint for such meta-analysis. Probably the most important criticism of these three meta-analyses is that they do not investigate differences in morbidity rather than mortality. In an editorial by Cook in the *Annals of Internal Medicine* he declared there are no clear winners and "original research is more likely to advance the field than additional meta-analyses" [Cook, 2001 #7].

Stemming from this statement as well as the introduction of new colloid solutions into anesthetic practice there have been several studies that have looked at potential differences in morbidity following the administration of a colloid versus a crystalloid. Gan et al studied 60 patients expected to have a blood loss of 500ml or greater. [Gan, 1999 #8] These patients were divided into three groups to receive either 6% hetastarch in lactate Ringers (Hextend, Abbott, Abbott Park, IL), 6% hetastarch in normal saline (Hespan) or lactated Ringers as their primary fluid to maintain intravascular volume based on hemodynamics, central venous pressure and urine output. Hospital stay, pain, postoperative nausea and vomiting, rescue antiemetics and subcutaneous edema was significantly less in the two groups receiving colloid. In a study of 200 cardiac surgical patients Bennett-Guerrero et al also compared crystalloid to colloid administration. [Bennett-Guerrero, 2001 #9] In this study the patients were divided into one of four groups to receive either 5% albumin in a normal saline vehicle, 6% hetastarch in normal saline (Hespan), 6% hetastarch in lactated Ringers (Hextend, Abbott, Abbott Park, IL) or lactated Ringers solution. They found that the patients receiving colloid had lower visual analog pain scores ($p < 0.0001$), decreased antiemetic use ($p< 0.001$) and less subcutaneous edema ($p< 0.001$). They also noted that the patients receiving colloid had a faster return of bowel function ($p < 0.001$). It is important to note that in both these studies patients in the colloid groups also received balanced salt solutions as part of their maintenance therapy. Based on these studies it would appear if, during the intraoperative period, there are likely to be major fluid shifts or large amounts of blood (> 500 ml) are likely to be lost, the combined use of both crystalloids and colloid will improve outcomes especially those related to GI motility, edema and pain.

It is important to note that not all crystalloid are the same. As noted in Table 1 there are significant differences in the composition of the various balanced salt solutions. Recent studies have more carefully investigated the impact of these differences in composition of these crystalloid solutions. Normal saline contains a significantly higher chloride load. It also lacks any form of buffering salt such as lactate or acetate. In addition lactated Ringers contains additional ions such as calcium. In the November 2000 issue of ANESTHESIOLOGY there were three lead articles as well as an Editorial on the impact of normal saline administration and the development of acidosis.Prough [Liskaser, 2000 #11] [Rehm, 2000 #12] [Waters, 2000 #13] In 1948 Shires and Holman put forth the hypothesis that saline administration results in dilutional acidosis. [Shires, 1948 #20] That is to say that as normal saline dilutes the blood volume there is a dilution of bicarbonate resulting in a more acidotic state. The editorial argues that the three studies published in the November issue all confirm that the mechanism of the acidosis is fully described by this dilutional effect. However, the articles themselves tend to imply that the changes in bicarbonate and pH are not entirely described simply by dilution. Irrespective of the mechanism of this metabolic acidosis the administration of normal saline results in a fairly significant metabolic acidosis that lasts over three hours and a significant hyperchloremia. Although these changes in acid base and fluoride ions are fairly small in magnitude they may not be benign.

Mythen et al conducted a study in patients over 60 years old in which they compared the effects of 6% hetastarch in normal (Hespan) to 6% hetastarch in Ringers lactate (Hextend, Abbott, Abbott Park, IL). [Pembrook, 2001 #15] The primary measured outcome variable was the incidence of hyperchloremic acidosis, which occurred in 67% of the patients receiving Hespan compared to none in the Hextend group at the conclusion of surgery. This was seen despite no differences in fluid volume, cardiovascular variables or estimated blood loss between the two groups. The authors also noted that there were significant differences in calcium and ionized calcium between the two groups. Patients in the Hextend group also had significantly better indices of end organ perfusion as measured by the gastric tonometer.

Wilcox et al demonstrated in the early 1980's that changes in plasma chloride markedly reduced renal blood flow up to 50%. [Wilcox, 1983 #16]In the study mentioned above by Bennett-Guerrero they also looked at perioperative renal function. In all four groups the total volume of fluid administered, cardiac output, blood pressure and preoperative serum creatinine were all similar ($p \geq 0.37$). However, there were significant differences in urine output four hours postoperatively, serum creatinine and creatinine clearance on postoperative day 7. In the two groups receiving normal saline, i.e., the 5% albumin and Hespan groups, creatinine had increased to an average of 1.5 ml/dL and creatinine clearance had decreased by approximately 30%. Probably the most significant finding was that six patients in the normal saline groups required hemodialysis postoperatively versus none in the lactated Ringers group. Although this was not a prospectively tested primary outcome variable its impact is so important that it cannot be ignored. This study obviously needs to be verified by follow-up studies that would confirm these results. A study by Scheingraber et al which investigated the incidence of dilutional acidosis in 24 women undergoing major intra-abdominal gynecological surgery also found in the group administered normal saline that there was a tendency toward lower urine outputs compared to the patients receiving lactated Ringers. [Scheingraber, 1999 #17]

A recent and important finding stemming from the studies comparing normal saline versus lactated Ringers especially when combined with 6% hetastarch has been changes in coagulation. Ref Gan In the very first study, which compared 6% hetastarch in lactated Ringers (Hextend, Abbott, Abbott Park, IL) to 6% hetastarch in normal saline (Hespan) in a subgroup of patients, the thromboelastogram was measured. It was noted in the patients' receiving large volumes of 6% hetastarch in normal saline (Hespan) that indices of decreased clotting especially prolongation of the time to onset of clot formation was seen. The patients receiving 6% hetastarch in normal saline also had a larger volume of red blood cell transfusion and trended to requiring more blood products. In addition in this group a significant number of patients required calcium supplementation compared to the 6% hetastarch group in Ringers lactate. In the study by Bennett-Guerrero et al in cardiac patients, those who received 6% hetastarch in normal saline required platelets or FFP in 69% of patients compared to 47% of patients in the hetastarch plus lactated Ringers. [Bennett-Guerrero, 2001 #9] In the albumin group the percentage of patients requiring platelets or FFP was 42% whilst in the lactated Ringers only group this was 26%. Interestingly by thromboelastography the patients in the lactated Ringers group were hypercoaguable and 8% had an incidence of DVT. In the study by Mythen et al they also noted a significant difference in the coagulation profile between 6% hetastarch in saline versus Ringers lactate. [Pembrook, 2001 #15] These data would tend to indicate that 6% hetastarch alters the clotting profile. Hetastarch diluted in lactated Ringers rather than normal saline tends to negate this hypocoaguable state probably by the addition of calcium, the prevention of the metabolic acidosis caused by normal saline and possibly due to changes in protein charge secondary to the acidosis. Interestingly lactated Ringers on its own may result in a hypercoaguable state as described by Bennett-Guerrero. [Bennett-Guerrero, 2001 #9] It will be important to confirm this effect of lactated Ringers with other studies and in non-cardiac patients.

The data presently available indicates that there are advantages to the appropirate use of colloids especially when combined with a balanced salt solution (i.e., lactated Ringers). As stated earlier the objective of intraoperative fluid administration is to optimize tissue perfusion. As such it would make sense that fluid administration directed at the goal of optimizing cardiac output would also enhance outcomes. Two recent studies have tended to confirm this. Mythen and Webb investigated 60 patients who were randomized to either a control group, which received standard practice administration of fluids versus a second group whereby fluid administration was optimized with the use of an esophageal Doppler monitor to maximize cardiac output. [Mythen, 1994 #21] At the end of surgery stroke volume was below its starting value in the control group whereas in the protocol group it was increased above baseline. In both groups at the end of surgery heart rate and blood pressure were similar between groups. Gastric tonometry, a measure of gut perfusion, was significantly decreased in the control group whereas it was maintained at preoperative values in the protocol group. The incidence of significant complications was significantly higher in the control group (6 vs. 0, p =0.01). Most significantly the incidence of ICU days decreased from 1.7 days in the control group to one day in the protocol group and the total length of hospital stay decreased from 10.1 in the control group to 6.4 in the protocol group (p=0.01). These data were subsequently confirmed in a study by Gan et al which investigated 100 ASA II and III patients with an expected blood loss of >500 ml. (? Ref) Intraoperative fluid was optimized in the study group again with the use of an esophageal Doppler monitor and this was compared to a control group receiving standard practice fluid administration consisting of both crystalloid and 6% hetastarch. The protocol group received a greater amount of colloid administration but the same volume of crystalloid. The length of hospital stay decreased significantly from 7 ± 5 days to 5 ± 3 days (p=0.03). This decrease in hospital stay appeared largely related to GI motility, as the control group were able to tolerate fluids only at 5 ± 4 days compared to 3 ± 2 days in the protocol group (p=0.01). The incidence of other side effects such as cardiovascular, respiratory, renal and wound infection tended to be lower in the protocol group but did not reach statistical significance. Rescue antiemetics were significantly higher in the control group.

In recent years there has been a an increase in studies taking a much closer look at fluid administration in the perioperative period. Although for some time the assumption has been that this has little impact on outcomes it would appear that the most recent studies have demonstrated that morbidity rather than mortality is significantly altered by both the type of fluid administered and how it is administered. The "take home" messages from these recent studies are A) the combination of both crystalloid and colloid is optimal for fluid administration especially when blood loss is likely to exceed 500 ml; B) Ringers lactate is the preferred crystalloid either alone or when used to dilute 6% hetastarch. C) Normal saline results in a significant metabolic acidosis, hyperchloremia, altered renal function and the potential in compromised patients to produce renal failure. D) When 6% hetastarch is combined with normal saline and greater than 2000 ml is administered it is likely to result in a hypocoaguable state with the potential for increased bleeding. This is prevented by diluting the 6% hetastarch in lactated Ringers. E) By combining crystalloid (for maintenance) and colloid (for replacement fluid) and administering these fluids to optimize cardiac output, outcomes, especially GI motility and hospital length of stay, are further enhanced.