GOAL DIRECTED PERIOPERATIVE FLUID MANAGEMENT – ROLE OF COLLOIDS.

DR.N.KANAGARAJAN,
SENIOR CONSULTANT,
DEPT OF CARDIAC ANESTHESIA,
ICVD, MADRAS MEDICAL MISSION HOSPITAL, CHENNAI.

Callum KG et al (1999)
'Errors in fluid management (usually fluid excess) were the most common cause of perioperative morbidity and mortality.

Introduction:

Perioperative fluid therapy is the subject of much controversy, and the results of the clinical trials investigating the effect of the fluid therapy on outcome of surgery seem contradictory. Hemodynamic management and appropriate fluid therapy remains a challenge in postoperative surgical patients. Hypovolemia results in inadequate cardiac output and reduced organ perfusion ,may lead to impaired microcirculation and multiorgan dysfunction. Intravenous fluid resuscitation is a key component in the treatment of surgical patients, to maintain the patient's physiological functions and to replace fluid lost.Fluid overload may be just as harmful as hypovolemia. Pulmonary edema may occur as a consequence of fluid overload even in patients without pre-existing cardiac disease.

The "Recipe Book" approach:

The traditional "recipe book" approach to fluid administration is based on the use of Standard fluid therapy which includes replacement of fluid lost [by basal fluid requirements, perspiration through surgical wound, loss to the third space and blood loss and exudation through the surgical wound] and maintenance of physiological functions ("preloading" of neuroaxial blockade). This approach takes no account of preoperative fluid status, the known inaccuracy of observation of blood and other fluid losses, or perioperative variation in myocardial function and vascular tone.

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. The total intravascular volume (or blood volume) is approximately 5L and has intracellular (40%) and extracellular (60%) components. Plasma is a solution in water of inorganic ions (predominantly Na,Cl), simple molecules such as albumin and the globulins. Water moves freely through cell and vessel walls and is distributed throughout all these compartments. The capillary endothelium is freely permeable to small ions such as Na^+, Cl^- but is relatively impermeable to larger molecules such as albumin and semisynthetic colloids which are therefore normally theoretically maintained in the intravascular fluid(space).

% OF TOTAL BODY WEIGHT.

Volume of TBW

	PLASMA 5%
	INTERSTITIAL FLUID 15 %
	INTRACELLULAR VOLUME 40 %

Extracellular volume	14,000ml	10,000ml
Plasma	3500ml	2500ml
Interstitial	10,500ml	7500ml
Intra cellular volume	28,000ml	20,000ml
	42,000ml	30,000ml

Pathophysiological changes in fluid and electrolytes

The metabolic reaction to injury involves important changes in fluid and electrolyte physiology. Salt (Na,Cl) and water are retained avidly in the first few days, called by Moore **'the sodium retention phase of injury'**. Convalescence and recovery are heralded by a return of the capacity to excrete any salt and water overload acquired during the earlier phase. The Transcapillary escape rate of albumin from the circulation into the interstitial space increases from 5 to 15% per hour after major surgery and may take up to 10 days to return to normal. Sepsis and other complications may prolong this period. This, and the vasodilatory effects of anaesthetic agents which increase the intravascular volume requirement (i.e. decrease the effective circulatory volume), have important therapeutic implications. Patients present for surgery with a variety of conditions that result in **altered fluid distribution.** Electrolytes deficiency may depend on the type of surgery and fluid lost.

I. WATER AND SOLUTE DEPLETION:

a)Decreased intake

- Fasting before surgery.
- Anorexia.
- Altered conscious level.

b)Increased losses
- Diarrhea / vomiting / pyrexia.
- Vasodilation.
  Due to anesthetic drugs leading to a reduction in the ratio between the circulating volume and the capacity of intravascular space.

c)Myocardial impairment:
Leading to a reduction in flow through the circulation.

d)Fluid shift:
Between compartments and may also reduce the circulating volume.

1. **The causes of increased capillary permeability:** During major surgical procedures include surgical tissue trauma, tissue hypoperfusion due to inadequate fluid therapy, ischemia/ reperfusion injury, sepsis and the all of extracorporeal circulation. They cause inflammatory stimuli that can compromise vascular integrity.

2. **Third space losses:**Fluid that is lost into the transcellular fluid spaces. These losses occur into spaces, such as bowel lumen and peritoneal and pleural cavities, which normally contains minimal volumes of fluid. In the presence of inflammation and breakdown of normal fluid compartment integrity, these spaces can fill up with non-functional extracellular fluid. Third-space losses are commonly associated with the inflammatory response to burns, trauma and surgery: they are a particular problem during major intraabdominal surgery and **may exceed 10ml/kg/hour**.

II. FLUID LOST DURING SURGERY:
a)Preoperative Fluid Deficit:

The pre-operative fluid deficit is calculated as following:

0-10 kg - 4ml/kg.

10-20 kg - 40 ml+2ml/kg for each kg more than 10 kg.   X No of fasting hours.

More than 20 kg - 60 ml + 1 ml/kg for each kg more than 20 kg.

b)The Insensible perspiration:

The insensible perspiration is approximately 10ml/kg/day in normal conditions, and this does not change much during surgery. About two thirds of the volume is lost through the skin and one-third from the airways which depend

on the humidity of the inhaled air. Inhalation of 100% water saturated air causes a loss close to zero, while dry air cause a loss of approximately 0.5ml/kg/hr. Patients are allowed to drink until 2 hours before elective surgery and should therefore be well hydrated.

c)Urine

A small dieresis (not less than0.5ml/kg/hour) is acceptable during surgery as long as hypovolemia is not the cause. Urine may be reduced, both because of the release of stress hormone reduce the excretion of salt and water and the anesthesia may cause hypotension. Hypovolemia should be avoided. It reduces both GFR and renal blood supply and may cause renal failure.

d)The evaporative loss:

The evaporative loss from the surgical wound depends on both the size of the incision and the exposure of the intestines.

- In minor incisions with slightly exposed but non- exteriorized viscera it is 2.1 g/hour
- In moderate incisions with partly exposed but non- exteriorized viscera it is 8.0 g/hour
- In major incisions with completely exposed and exteriorized viscera it is 32.2 g/hour.

The loss is independent of the body weight. The loss from completely exteriorized viscera decreases by 50%after 20 min and wrapping the exteriorized viscera in plastic reduce the loss by 87.5%.

Type of Secretion	Volume (mL/24 h)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	HCO_3^- (mEq/L)
Stomach	1000–2000	60–90	10–30	100–130	0
Small intestine	2000–3000	120–140	5–10	90–120	30–40
Colon		60	30	40	0
Pancreas	600–800	135–145	5–10	70–90	95–115
Bile	300–800	135–145	5–10	90–110	30–40

e)The loss to *third space*:

1)Pathological Fluid Accumulations: Occur before, during, or after surgery. The diseases and /or trauma may cause fluid to accumulate in a transcellular to interstitial space and cause an expansion of the ECV. A volume of ascitic or pleural fluid emptied through drains during surgery or in the postoperative period can be accurately measured and will cause a postoperative weight loss, and this can be replaced with appropriate fluid orally or intravenously. The volume of the fluid accumulated in the interstitial space of traumatized tissue is more difficult to assess, and is highly influenced by the type of intravenous fluid administered.

2)The non-anatomical third space loss (or deficit in functional extracellular volume).The surgical trauma per se causes a contraction of the ECV, with a volume of extracellular fluid sequestered in a compartment. The anatomical location of the missing fluid was not clear. The loss to the third space is replaced according to algorithms. Volumes up to 15ml/kg/hour are recommended in the first hour of abdominal surgery, with decreasing volumes in subsequent hours.

f)Replacement of lost blood:

Replacement of lost blood with a crystalloid demands infusion of almost triple volume because crystalloid is dispersed throughout the entire extracellular space. This causes an expansion of the interstitial space, with postoperative edema formation and body weight gain. Alternatively, a colloid that stays in the vascular space for a longer time seems to be a more expedient choice for replacement of lost blood.

g)Exudation from surgical wound:

Exudation from the surgical wound is often lost in the surgical dressings and its volume is based on an estimate, but it will show as a postoperative weight change. The exudates contain protein and manipulation of the intestines increases the protein loss.

h)The maintenance of physiological functions:

Neuroaxial blockade causes a relaxation of the vascular bed innervated by the affected segments of the spinal cord. This causes a decrease in peripheral vascular resistance with a decrease in arterial blood pressure. It is common to respond to this decrease in blood pressure by giving either 500 of colloid or 1000ml of crystalloid intravenously.Co hydration with fluids with vasopressor agent are best way to manage hypotension during neuroaxial blockade

III. FLUID THERAPY:

Choice of fluid in clinical practice should be guided by an understanding of the physiochemical differences and their distribution within the physiological compartments of the body. The balance between inadequate fluid resuscitation and decreased tissue perfusion and excess fluid with edema formation will vary for specific types of surgery. 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 necessary volumes of crystalloids or colloids (more logical choice) will be effective. Prolonged cavity surgery with significant evaporative losses would additionally require replacement of water in the form of 5% glucose.

1. Preoperative Fluid Therapy:

The pre-operative fluid deficit is calculated according to the formula. Both perspiration and deficit from fasting, primarily involves the loss of water and replacement with water preparation like glucose 5% seems logical. The pre-operative deficit + maintenance fluid should be either glucose containing or non-glucose balanced solutions.50% of total calculated pre-operative fluid deficit should be given in the 1st hour and remaining 25% in 3rd hour. The maintenance fluid and the fluid which is lost during surgery should be replaced along with this.

The Holliday and Segar formula: the average maintenance requirement for fluid

Body weight(kg)	Average maintenance allowance for fluid	
	ml per day	ml per hour
0-10	100ml per kg	4 ml per kg
10-20	1000 ml +50 ml per kg for each kg more than 10 kg	40 ml + 2 ml per kg for each kg more than 10 kg
20-30	1500 ml+20 ml per kg for each kg more than 20 kg	60ml+1 ml per kg for each kg more than 20 kg

2. Blood transfusion:

Management of potential to actual blood loss includes
- o Monitoring the amount of blood loss (suctioning and sponge)
- o Monitoring hemoglobin and hematocrit
- o Monitoring for the presence of in adequate perfusion and(BP,HR,MVO2)
- o RBC and autologous blood transfusion.
- o RBC transfusion algorithm
  - ▪ Hb < 6 g/dl — RBC transfusion is reasonable and life saving
  - ▪ Hb < 7 g/dl — Reasonable in most post-operative patients.
 - ▪ Hb > 10 g/dl — Not recommended.

IV. TYPES OF FLUID:
  a)Crystalloid.
  b)Colloids.

a)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. Potassium, calcium and lactate may be added to more closely replicate the ionic makeup of plasma. The small amount of glucose in the isotonic solutions is rapidly metabolized, thus allowing the solvent water to freely distribute throughout total body water.

Intravenous fluid	Sodium (mmol/litre)	Osmolality (mosm/kg H2O)	%Electrolyte Free Water
DEXTROSE 5%	0	252	100
SALINE 0.18%/DEXTROSE 4 %	30	282	80
SALINE 0.45%/DEXTROSE 2.5 %	75	293	50
HARTMANN'S SOLUTION	131	278	16
DEXTROSE 5 %/RINGER'S SOLUTION	130	525	16
SALINE 0.9%	150	308	0
DEXTROSE 5%/SALINE 0.9%	150	560	0

SODIUM CONTENT AND OSMOLALITY OF COMMONLY USED CRYSTALLOID SOLUTIONS
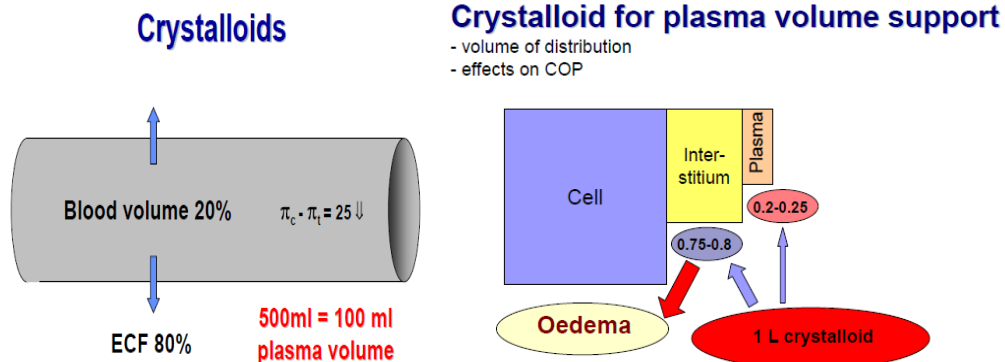
b) Colloid Solutions:

Colloid contains high molecular weight molecules, either natural or synthetic and has an oncotic pressure   similar to that and plasma. 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. Colloids remain within the intravascular space for a relatively long time and are used to sustain blood pressure and to avoid complications from fluid overload. The duration of Plasma Volume Expansion produced by each colloid is governed by the rate of colloid molecule loss from the circulation and by their metabolism. The most useful descriptors of magnitude and duration of PVE are the intravascular half-life and fraction of administered volume retained in the circulation after a specific time.

COLLOID SOLUTIONS used in clinical practice for fluid therapy are divided into
- Semi synthetic colloids
    1) Gelatins
    2) Dextrans
    3) Hydroxyl ethyl starch

- Naturally occurring human plasma derivatives
    1) Human albumin solutions
    2) Plasma protein fraction
    3) Fresh frozen plasma
    4) Immuno globulin solutions

Isotonic Colloid
(assuming no capillary leak)

Blood volume 100% $\pi_c - \pi_t = 25 \Rightarrow \Uparrow$

ECF 0%   **500 ml = 500 + ml plasma volume**
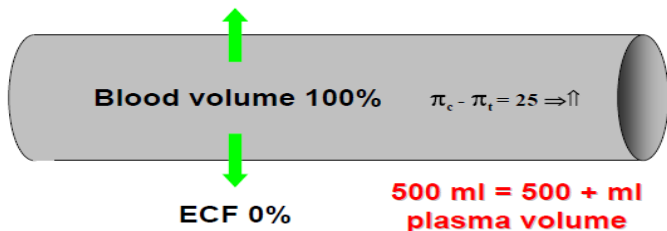
1)Natural colloids:

Albumin:

Albumin is a widely used naturally occurring plasma protein. Albumin is derived from pooled human plasma and there should be no risk of disease transmission as albumin is heated and sterilized by ultrafiltration. It is generally considered to be safe. The molecular weight of albumin ranges from 66000 – 69000 dalton. 5% albumin is iso oncotic, where as 20% and 25% solutions are markedly hyper oncotic so that total plasma volume is expanded by translocation of fluid from the interstitial to the intravascular compartment. The effects of 5% albumin are not well predictable: infusion of 500 ml of albumin may expand plasma volume by 490 ml of 750 ml. Since maintenance of COP is postulated to be desirable goal of volume replacement, albumin is still given in patients with low output syndrome due to hypervolemia or heart failures. In patients with altered vascular endothelial integrity (after CPB, in sepsis) albumin may pass into the interstitial space, by which fluid shift from the intra vascular compartment may be promoted and interstitial volume is substantially increased. In most countries, the use of albumin in the management of hypovolemia is relatively uncommon because the semi synthetic colloids are believed to at **least as effective.** Recent reports from a 7000 patients multi center RCT of critically ill patients in Australia suggested that there was no difference in mortality between patients managed with albumin or 0.9% NaCl.

2)Semi Synthetic colloids:

a)Dextrans

Dextrans are linear polysaccharide molecules of high molecular weight. Two different preparations are available: 6% dextran 70 (average molecular weight 70 KD) and 10% dextran 40 (average molecular weight 40 KD). Increase in plasma volume alter infusion of 1000ml of dextran 70 ranged from 600 – 800 ml. Infusion of dextran 40 has been described to increase microcirculatory flow because of a reduced red cell and platelet sludging, volume expansion and hemodilution – induced reduction in whole blood viscosity. **Dextrans are associated with severe anaphylactic reactions, coagulation abnormalities and impaired blood cross matching.**

Characteristics of dextran solutions

	6% Dextran 70	10% Dextran 40
Mean molecular weight (Dalton)	70,000	40,000
Volume effect(hours)(Approx.)	5	3-4
Volume efficacy(%)(approx.)	100	175-(200)
Maximum daily dose(g/kg)	1.5	1.5

b)Gelatins

The increase in blood volume is approximately the same as that of the infused volume of gelatin (range 70% - 90%). Due to low molecular weight, plasma half-life (two to three hours) so that reinfusions are necessary to maintain blood volume sufficiently with regard to volume effect. Gelatins are the **least effective colloid** . Also they are having the **high incidence of severe anaphylactic reactions.**

Characteristics of Gelatin solutions

	Urea-cross-linked gelatin	Cross-linked gelatin	Succinylated gelatin
Concentration (%)	3.5	5.5	4.0
Mean molecular weight(Dalton)	35000	30000	30000
Volume effect(hours)(approx.)	1-3	1-3	1-3
Volume efficacy(%)(approx.)	80	80	80
Osmolarity(approx)	301	206	274

c)Hydroxyethyl Starches(HES)

Concentration:

Concentration mainly influences the initial volume effect: 6% HES solutions are iso-oncotic *in vivo*, with 1 L replacing about 1 L of blood loss, whereas 10% solutions are hyperoncotic, with a volume effect considerably exceeding the infused volume (about 145%).

CHARACTERISTICS OF HYDROXY ETHYL STARCH (HES) SOLUTIONS.

	HES 70/0.5	HES130/0.4	HES200/0.5	HES 200/0.5	HES 200/0.62	HES 450/0.7
CONCENTRATION(%)	6	6	6	10	6	6
VOLUME EFFICACY(%) (APPROX)	100	100	100	130	100	100
VOLUME EFFECT(HOURS) (APPROX)	1-2	2-3	3-4	3-4	5-6	5-6
MEAN MOLECULAR WEIGHT (kD)	70	130	200	200	200	450
MOLAR SUBSTITUTION(MS)	0.5	0.4	0.5	0.5	0.62	0.7
C2/C6 RATIO	4:1	9:1	6:1	6:1	9:1	4.6:1

Molecular Weight: In common with all of the synthetic colloids, HES are polydisperse systems containing particles with wide range of molecular mass.When a polydisperse colloid is infused into the circulation, small molecules below the renal threshold (45 to 60 kDa) are rapidly excreted, whereas the larger molecules are retained for varying periods of time depending on their size and ease of breakdown. However, osmotic effectiveness depends on the number of particles, and not the molecular size; therefore, the excretion of the smaller particles continuously reduces the osmotic effectiveness of the infused solution. This is compensated for by the continuous supply of oncotically active molecules arising from degradation of larger fragments. Mean MW of the available products ranges from over 670 kDa to 70 kDa.

Molecular Substitution:HES have a varying number of hydroxyethyl residues attached to the anhydrous glucose particles within the polymer. This substitution increases the solubility of the starch in water and, to a varying degree, inhibits the rate of destruction of the starch polymer by amylase. As with MW, there are two methods for calculating the degree of substitution on the starch polymer. The first of these is termed the **degree of substitution** and is calculated from the number of substituted anhydroglucose residues divided by the total number of anhydroglucose residues. **DS=Gs/Gt** (**DS**-degree of sustitution,**Gs** - number of substituted anhydrous molecules and **Gt** -the total no of anhydrous residues in the polymer. The second is **MS**, the average number of hydroxyethyl residues per glucose subunit. The figure 0.7 in the description of a HES preparation indicates that there are seven hydroxyethyl residues

on average per 10 glucose subunits. hexastarch (MS = 0.6), pentastarch (MS = 0.5), and tetra starch (MS = 0.4). Unsubstituted anhydroglucose units are more prone to enzymatic degradation by α-amylase; therefore, hydroxyethylation slows down the rate of enzymatic breakdown of the HES molecule and prolongs intravascular retention time

$$MS = \frac{W_H}{1 - W_H} \times \frac{162}{44}$$

W_H -- weight fraction of the hydroxyethyl groups in the polymer. The number represents the mass of the hydroxyethyl group (44) and the anhydrous glucose residue (162) respectively.

C2/C6 Ratio:

Hydroxyethylation of the glucose subunits is guided predominantly towards the C_2 and C_6 carbon atoms. Hydroxyethyl groups at the position of the C_2 atom inhibit the access of α-amylase to the substrate more effectively than do hydroxyethyl groups at the C_6 position. Hence, HES products with high C_2/C_6 ratios are expected to be more slowly degraded.
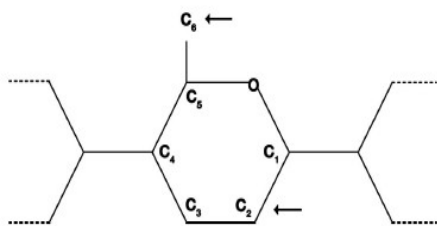

Fig. 1. Hydroxyethyl substitution of hydroxyethyl starch (HES) glucose subunits takes place preferentially at the C_6 and C_2 positions.
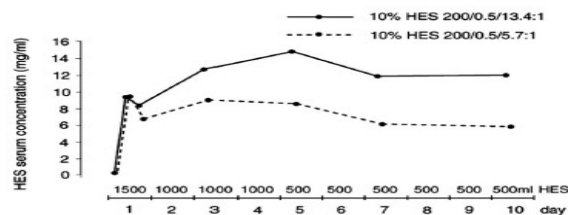
Fig. 2. Different effects on serum concentration during 10-day hemodilution therapy of two pentastarches with different C_2/C_6 ratios: 10% hydroxyethyl starch (HES) 200/0.5/13.4:1 and 10% HES 200/0.5/5.7:1. (Comparison between the two HES preparations from the third timepoint on day 1 is $P < 0.01$). Reprinted with permission from Treib J, *et al.*[11]

Volume effects of different plasma substitutes (500mL)

(Kröll et al., 1993)
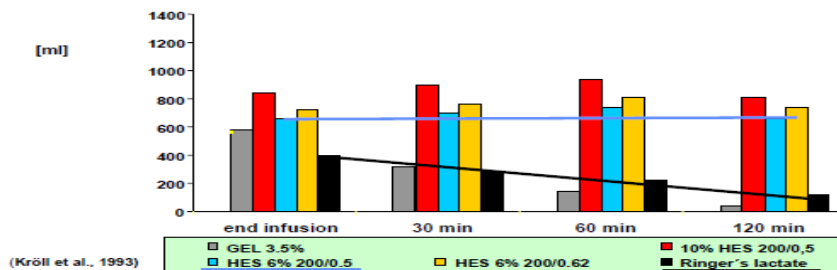
Third-Generation HES: Tetra starch

The development of newer starch-based plasma volume expanders has been driven by a need to improve safety and pharmacological properties while maintaining the volume efficacy of previous HES generations. Reductions in MW and MS have led to products with shorter half-lives, improved pharmacokinetic and pharmacodynamics properties, and fewer side effects.

SAFETY PROFILE:

1. Effect on Coagulation and Platelet Function

Overall, the more rapidly degradable HES products have been found to have a greatly reduces effects on the coagulation process compared to older products. HES macromolecules interact with platelets and the coagulation cascade, causing a decrease in factors such as Factor VIII and von Willebrand factor, but the exact mechanisms have still not been fully elucidated. In a study on 30 patients with cerebrovascular disease patients were randomized to receive daily infusions with up to 1.5 l of 6% HES 200/0.62, 10% HES 200/0.5, or 6% HES 40/0.5. Platelet count was significantly decreased in all three groups, but the largest drop was seen in the HES 200/0.62 group. The authors speculate that HES macromolecules attach to platelets or are phagocytized by them. In one high-dose study, Ellger *et al(49)* found that 6% HES 130/0.4, when given up to 50 ml/kg, had similar effects on coagulation as 30 ml/kg HES 200/0.5 plus gelatin. In this study, 40 patients undergoing elective surgery for urology-related cancer were randomized to receive one of the HES preparations. Similar results were obtained in a study of 120 patients undergoing elective coronary artery bypass surgery(50).Patients were randomized to volume replacement either with 6% HES 130/0.4 (up to 50 ml/kg) or 6% HES 200/0.5 (up to 33 ml/kg) with volume requirements in excess of these doses being met with gelatin. Despite being used at a median dose of 49 ml/kg, HES 130/0.4 did not increase blood loss and transfusion requirements compared to the lower dose of HES 200/0.5. Kozek-Langenecker *et al* concluded that HES 130/0.4 was associated with a significant reduction in perioperative blood loss, both estimated and calculated, and that there was a significant reduction in transfusion needs. The reduction in the volume of erythrocyte loss and in transfusion needs was in the order of one red blood cell unit for both parameters. These studies confirm that, unlike earlier generation HES preparations, **the tetra starches have minimal effect on coagulation(HES 30/0.4).**

2. Accumulation and Tissue storage

Due to the more rapid clearance of the latest generation of tetrastarches, it is expected that tissue accumulation and its clinical manifestations will not be observed with the same frequency as compared to older starches. Numerous reports based on human biopsy can be found to indicate that early generation HES products accumulate in various tissues, including liver, skin, cutaneous nerves, and possibly the placenta. In healthy volunteers, Waitzinger *et al.* demonstrated that 6% and 10% solutions of HES 130/0.4 showed no clinically relevant accumulation in plasma either after single doses or after repetitive infusion over 10 days. The main clinical manifestation of tissue storage is HES-related pruritus, arises from long-term cutaneous storage of HES molecules, and it may last for months after exposure. It is resistant to treatment by glucocorticoids, antihistamines, acetaminophen, and neuroleptic drugs**. In other studies of HES 130/0.4 using relatively high doses, pruritus did not seem to be a clinical problem.**

3. Effect on Plasma bilirubin

Waxy maize-derived HES 130/0.4 has been extensively studied and not associated with deterioration of liver function compared to controls. One study with potato-derived HES (130/0.42) reported mild to moderate hyperbilirubinemia as a significant adverse event (74).**Potato-derived HES 130/0.42 are the only tetra starch to be absolutely contraindicated in patients with severe hepatic impairment.**

4. Effect on renal function

More recent studies using third-generation products have not reported unfavorable effects, suggesting that the lower tendency of these products to accumulate may improve their profile with regard to renal function. An important large-scale observational study of the effects of HES administration on renal function was carried out by Sakr *et al.* In a retrospective analysis of data of 3,147 critically ill patients included in the SOAP study (Sepsis Occurrence in Acutely Ill Patients), it was found that HES *per se* was not an independent risk factor for adverse effects on renal

function in the 1,075 patients who received HES. Neither the use of HES nor the dose administered was associated with an increased risk of renal replacement therapy, even in the subgroup of patients with severe sepsis and septic shock (n = 822). They did acknowledge that the use of newer HES preparations with a lower tendency to accumulate may have contributed to the favorable results. In the considerable body of clinical data on the third-generation HES 130/0.4, there have been no reports of adverse effects on renal function over and above those seen in control groups in patients who are considered to be at particular risk, such as those with previous mild to severe renal dysfunction the elderly, and those receiving high-dose therapy.

Nine clinical trials on renal function demonstrate the safety of waxy maize-derived HES 130/0.4, and two recently published trials confirm that potato-derived HES 130/0.42 has no adverse effects on renal function.

5. Specia patient groups

Due to a higher incidence of comorbidities and changes in lung, kidney and cardiovascular function, the elderly are at increased risk for impairment of renal function. The waxy maize-derived tetra starch HES 130/0.4 has been thoroughly studied in these groups and has a well-documented safety profile. In cardiac surgery patients, HES 130/0.4 was deemed to be as safe as gelatin offering a more persistent volume effect and a lower risk of anaphylactic reaction. **Waxy maize-derived HES 130/0.4 is the only third generation HES with controlled clinical data in children**. In this context, Standl *et al*. reported that waxy maize-derived 6% HES 130/0.4 was as safe and well tolerated as albumin when used in pediatric surgery.

6. Effect on microcirculation and Oxygenation

Third generation HES 130/0.4 has positive effects on tissue oxygenation and microcirculation in patients undergoing major abdominal surgery. Intravascular volume replacement with a 6% solution improved tissue oxygenation compared with a crystalloid-based volume replacement strategy using lactated Ringer's titrated to similar hemodynamic endpoints. Lang *et AL* attribute these beneficial effects of tetra starches to improved micro perfusion and reduced endothelial swelling; crystalloids mostly distribute in the interstitium, causing endothelial tissue swelling and reduced capillary perfusion.

7. Effect on Systemic Inflammation and Endothelial activation

Surgery triggers a systemic inflammatory response with the release of inflammatory mediators into the systemic circulation. In a study of patients undergoing abdominal surgery, Lang *et al(101)* found a significantly lower increase of the proinflammatory cytokines IL-6 and IL-8 in patients receiving 6% HES 130/0.4 compared to those receiving lactated Ringer's solution. Likewise, in patients undergoing major abdominal surgery, Boldt *et al (91)* reported a similar attenuation of plasma levels of IL-6 in patients receiving 6% HES 130/0.4 compared to those receiving 5% albumin. Boldt speculates that the beneficial effect of HES 130/0.4 on inflammation and endothelial activation may be the result of some direct, substance-specific effects on endothelial cells resulting in reduced release of adhesion molecules. Synthetic colloids inhibit neutrophil adhesion by a neutrophil-dependent mechanism rather than interfering with endothelial cell activation.

V)CARRIER SOLUTIONS:

The two types of solution in current use are 0.9% saline and "balanced" solutions that aim to mimic the biochemical composition of human plasma.

Hyperchloremic Metabolic Acidosis:

Infusion of high volumes of normal saline may lead to the development of hyperchloremic metabolic acidosis, due to the high chloride load rather than to dilution of bicarbonate. It seems that it typically occurs only after the infusion of more than 3 l of normal saline; for patients receiving 2 l or less of a normal saline solution, there is only modest or no. Although disturbance of the acid-base balance can certainly be observed in patients receiving high volumes of saline, its clinical relevance are unclear .Some researchers suggest that it is benign and self-limiting. Others are convinced that it may impair renal and splanchnic perfusion as indicated by reduced urine flow, abdominal

discomfort or impaired gastric mucosal perfusion. It has been suggested that balanced solutions may be more beneficial in terms of blood coagulation and platelet function. Boldt *et al.* enrolled 30 patients scheduled for major abdominal surgery into a study where they were randomized to receive the potato-derived tetra starch, 6% HES 130/0.42 in either a balanced solution (Tetraspan®) or in saline (Venofundin®). Concomitant crystalloids in the two groups were also either balanced or saline-based, respectively, and were given in a 1:1 ratio with the associated colloid. The two groups showed no difference in terms of hemodynamics, coagulation measures or kidney function, but the mean base excess was significantly more negative in the group receiving the saline-based fluids.

In a study involving 81 patients undergoing elective valve surgery or coronary artery bypass grafting, the waxy maize-derived tetra starch HES 130/0.4 was compared in two forms, either in a saline solution **(Voluven®)** or in a balanced solution **(Volulyte®)**.The authors concluded that it is probably unnecessary to use balanced solutions if only moderate infusions are required, whereas **balanced colloids can be used to reduce chloride load when large volumes are required.**

VI) **Monitoring fluid therapy:**

1)Static variables of preload and fluid responsiveness

a)Cardiac filling pressures:

The trends in CVP during anesthesia and surgery are also useful in estimating fluid or blood loss and guiding replacement therapy.CVP and PAWP are frequently used to guide administration of fluids.Frank- Starling curve determining the ventricular preload/stroke volume relationship in every individual patient is not static, but changes in the shape of the individual curve (rightward/leftward shift) in response to impaired or enhanced left ventricular function may occur. Furthermore, filling pressures are highly dependent on left ventricular compliance that is frequently altered in critically ill patients. Consequently, the relationship between cardiac filling pressures and end diastolic volumes is curvilinear and may vary between individuals. The increase in intrathoracic pressure (positive pressure ventilation) is accompanied by an increase in pericardial pressure and secondarily by an increase in cardiac filling pressures, suggesting an inappropriate and potentially detrimental therapy. To summarize, static cardiac filling pressures, although still recommended to guide fluid therapy, are not appropriate to assess intravascular volume status, and moreover are not reliable predictors of fluid responsiveness.

b)Static volumetric variables

i)Left ventricular end-diastolic volume obtained by echocardiography

Preload is defined as the myocardial fibre length at end diastole. Therefore, an ideal clinical correlate should be left ventricular end-diastolic volume. Left ventricular end-diastolic volume obtained by TOE has been introduced as a clinical variable to assess preload. Although echocardiography can provide an excellent estimate of preload, one fundamental limitation using TOE in daily clinical routine is the need for costly equipment and training. Also, TOE is not suitable for monitoring patients continuously for a long period of time.

ii)Global end-diastolic volume(GEDV) obtained by Trans pulmonary thermo dilution

The PiCCO [continuous cardiac output based on pulse contour analysis, offers the possibility of assessing GEDV as a static volumetric variable of preload .Today, several investigations in both adults and infants are available which highlight the clinical significance of GEDV as an indicator of preload and potentially as a variable to predict fluid responsiveness with acceptable sensitivity and specificity. The application of GEDV, as a volumetric variable based on trans pulmonary thermo dilution technique, is not limited by spontaneous breathing efforts. As a large percentage of patients in the intensive care unit cannot be monitored by dynamic variables of fluid responsiveness due to spontaneous breathing, GEDV may be particularly useful under these circumstances and only GEDV was able to reflect both actual preload and fluid responsiveness.

2)Dynamic variables of fluid responsiveness

The basic principle of a dynamic approach to elucidate the individual Frank-Starling curve at the bedside is to induce a cyclic change in cardiac preload induced by mechanical ventilation.

a) Systolic pressure variation:

The arterial systolic pressure variation (the difference between maximal and minimal systolic arterial pressure values during one mechanical breath) and its Δdown component (Δdown¼ apnoeic – minimum systolic blood pressure) have been shown to be sensitive indicators of hypervolemia. Using the systolic pressure during apnoea as a reference point or baseline, the increase in systolic pressure above baseline during the respiratory cycle has been defined as Δup, and the decrease in systolic pressure below baseline has been defined as the Δdown component. The overall SPV is therefore the sum of Δup and Δdown.

b) Pulse pressure variation and stroke volume variation:

The algorithm used by the PiCCO system enables continuous calculation of SV by measuring the systolic portion of the aortic pressure waveform and dividing the area under the curve by the aortic impedance. Initially, the specific aortic impedance is determined by transpulmonary thermodilution. Based on the beat-to-beat measurement of pulse-contour-derived SV, SVV can be derived continuously from the mean values of four minimum and maximum SVs averaged during the previous 30 seconds. The respiratory variations of the arterial pulse pressure can be calculated accordingly.

c) Conditions affect the dynamic variables:

1. Effect of tidal volume
Cyclic changes in left ventricular stroke volume induced by positive pressure ventilation are based on cyclic changes in intrathoracic pressure and in lung volume. Consequently, the higher the magnitude of tidal volume applied, the more pronounced should be the effect on dynamic variables of fluid responsiveness, independently of intravascular volume status.

2. Effect of open-chest conditions
The effect of positive pressure ventilation on the cyclic changes in left ventricular preload is fundamentally influenced by the integrity of the chest. The cyclic changes in intrathoracic pressure should be decreased if the chest is opened, and consequently the effect on dynamic variables of fluid responsiveness should be less pronounced.

3. Influence of intra-abdominal hypertension
Intra-abdominal hypertension (IAH) is associated with a mechanical impairment of venous return as the result of inferior vena cava compression. Consequently, dynamic variables of fluid responsiveness must also be altered in the presence of IAH. In another experimental trial, Renner et al demonstrated that during IAH, SVV failed to predict fluid responsiveness, whereas PPV and GEDV preserved their ability to be reliable predictors of fluid responsiveness.

4. Influence of elevated positive end-expiratory pressure
Increasing PEEP primarily distends the lungs and increases intrathoracic pressure. Consequently, initially venous return is reduced, and this effect is more pronounced during hypovolaemia. It has been shown by Kubitz et al that increasing PEEP levels increased both PPV and SVV during closed- and open chest conditions. GEDV was sensitive and specific predictors of fluid responsiveness even during elevated PEEP levels, in contrast to PPV and is the only variable that yielded comparable threshold values at different PEEP levels.

5. Influence of norepinephrine
It has been suggested that vasopressors might exert a direct effect on regional vascular capacitance and that they would alter PPV and SPV and interfere with their ability to predict fluid responsiveness.

6. Influence of spontaneous breathing activity

One basic requirement for the assessment of dynamic variables of fluid responsiveness is positive pressure ventilation. Whether changes in intrathoracic pressure during spontaneous breathing and/or under positive pressure support ventilation might be insufficient to adequately modify loading conditions is still a matter of debate.Soubrier et al demonstrated that PPV and SPV are less reliable to predict fluid responsiveness during spontaneous breathing.

d)Perioperative optimization of fluid therapy guided by dynamic variables

It has been shown repeatedly that maximizing SV by fluid loading during high-risk surgery decreases the incidence of postoperative complications and the length of stay in the ICU and in the hospital. Lopes et al were the first to show in a small number of patients undergoing high-risk surgery that monitoring and optimizing PPV by fluid loading improves outcome and decreases the length of stay in the hospital compared to an unspecific fluid management protocol.

VII) GOAL DIRECTED FLUID ADMINISTRATION: HOW PERIOPERATIVE FLUID BALANCE INFLUENCES POSTOPERATIVE OUTCOME.

Goal directed plasma volume expansion during the intraoperative period is associated with improved outcome and reduction in hospital stay in patients undergoing cardiac and major orthopedic surgery.

Targets and Evidence for goal directed fluid therapy:

1. Cardiac Output:
There are various methods of Cardiac output monitoring modalities are there:

The Esophageal Doppler monitor (EDM) is that permits rapid, minimally invasive and continuous estimation cardiac output (g). The EDM monitor waveform that represents the velocity of blood flow within the decending thoracic aorta. The total amount of lime that blood is traveling in a forward direction within the aorta is the systolic Flow Time (FT). This is corrected for heart rate to give the corrected flow time (FTc).The FTc has been shown to be a good index of systemic vascular resistance and is to changes in left ventricular preload (h). Fluid challenge with a of 6% hydroxyethyl starch in saline was used to increase the FTc above 0.4 with no change in stroke volume. (Fluid challenge was given every 15 min). The FTc was kept at target values. [Wakeling HG et al, BJA   2005 95: 634-42]

2. Hemodynamic variables triggering fluid administration

- Urinary output 0.5 ml/kg/hr.
- An increase in heart rate more than 20% above baseline or more than 110 beats / min
- A decrease in mean systolic blood pressure less than 20% below baseline or less than 90mmHg. (Boluses of 200 ml fluid administered to the targets)

3. Other **non-invasive methods /devices** that may also be useful for goal directed intraoperative fluid administration.The routinely measured standard cardiovascular variables such as blood pressure, heart Rate, and O_2 saturation are unreliable in duration of mild hypovolemia.

4. Mixed venous O_2 saturation

a)Kimberger O et al(2009)
Goal directed colloid administration improves the microcirculation of healthy and Peri anastomotic colon
Anesthesiology 110(3); 496-504.
They compared the effects of goal directed colloid fluid therapy with goal directed crystalloid and restricted crystalloid fluid therapy on healthy and peri anastomotic colon tissue in a pig model of colon anastomosis surgery. **Their target was Mixed venous saturation (MVO₂) of >60%.**Goal directed colloid therapy involved continuous infusion of RL at the rate of 3ml/kg/hr. and If MVO_2 <60% bolus of 200 ml of colloid (HES 130/0.4).Heart rate, mean arterial pressure, central venous pressure, mean PAP and PCWP were recorded. A Thermodilution method

was used to measure cardiac output every 30 min. Mixed venous O_2 saturation was continuously with fiber optic catheter. They **CONCLUDED** that Goal directed colloid fluid therapy significantly increased microcirculatory blood flow and tissue oxygen tension in healthy and injured colon compared to goal directed or restricted crystalloid fluid therapy. Improved patient outcome is primarily caused by improved perioperative intestinal microcirculatory blood flow and increased tissue O_2 tension due to colloid fluid administration.

b)Donati A et al(2007)

Goal directed intraoperative therapy reduces morbidity and length of hospital stay in high risk surgical patients.
                                                                    Chest; 132; 1817 – 1824 .
This is a randomized, controlled trial in which 135 high risk patients scheduled for major abdominal surgery were studied. All patients were managed to achieve standard goals: mean arterial pressure >80 mmHg and urinary output > 0.5 ml/kg/hr. The protocol group of patients were also managed **to keep O_2ER <27%**,by an algorithm involving a fluid challenge(colloids to keep the CVP of 10 mmHg),dobutamine,packed RBCs to keep the hemoglobin 10g/dl. Their **conclusion** was Early treatment directed to maintain O_2ER at < 27% reduce organ failures and hospital stay of high risk surgical patients.

c)Lowell JA, Schifferdecker C, Driscoll DF et al (1990).

Prospectively monitored 48 consecutive patients admitted to an ICU postoperatively. They found that the 40% who gained >10% weight from preoperative or premorbid records, indicative of fluid overload had significantly greater morbidity and length of ICU stay. Mortality in the patients who gained >10% body weight was31.6% (versus 10.3% in the group that gained <10% body weight) and increased with greater weight gain, with patients who   gained >20% body weight having a mortality rate of 100%.

SUMMARY AND CONCLUSIONS

Perioperative fluid therapy has a direct bearing on outcome, and prescriptions should be tailored to the needs of the patient. The goal is to **maintain the effective circulatory volume while avoiding interstitial fluid overload** whenever possible. Third generation HES (waxy maize starch- HES 130/0.4) are suitable to achieve this goal. Weight gain in elective surgical patients should be   minimized in an   attemptto achieve a '**zero fluid balance status**'.

CRYSTALLOIDS AND COLLOIDS		
	Crystalloids	**Colloids**
Intravascular persistence	Poor	Good
Hemodynamic stabilization	Transient	Prolonged
Required infusion volume	Large	Moderate
Risk of tissue edema	Obvious	Insignificant
Enhancement of capillary perfusion	Poor	Good
Risk of anaphylaxis	-	Low to moderate
COP	Reduced	Maintained
Cost	Inexpensive	More expensive

Crystalloids and Tetrastarches should be used judiciously.

Further Reading:

1. Sibylle A. Kozek,Langenecker(2009). Influence of fluid therapy on the haemostatic system of intensive care patients. Best Practice & Research Clinical Anaesthesiology; 23 : 225–236.

2. Jochen Renner et al (2009). Monitoring fluid therapy. Best Practice & Research Clinical Anesthesiology; 23: 159–171.

3. A M. Roche, et al (2009).Goal-directed fluid management with trans-esophageal Doppler.Best Practice & Research Clinical Anesthesiology;23:327–334.

4. Westphal et al(2009).Hydroxyethyl Starches -Different Products – Different Effects Anesthesiology 2009;111:187–202

5. Kapoor PM et al(2008). Early Goal directed fluid therapy in moderate to high risk cardiac surgery patients.Annals of Cardiac anesthesia;11(1):27-34

6. Chappell D et al(2008).A Rational Approach to Perioperative Fluid Management. Anesthesiology 2008;109:723-40.

7. Gandhi DS et al (2007).Volume replacement therapy during major orthopedic surgery using Voluven ®(hydroxyethyl starch 130/0-4) or Hetastarch.Anesthesiology;106:1120-7.

8. Marik EP,Baram M and Vahid B(2008)Dose central venous pressure predict fluid responsiveness.Chest;134:172-78.

9. DN Lobo et al(2008).How perioperative fluid balance influences postoperative outcomes.Chest;134:172-78.

10. Brandstrup B(2006).Fluid therapy for the surgical patients.Best practice and research clinical anesthesiology; 20(2) 265-283.

11. Grocott et al (2005).Perioperative fluid management and clinical outcomes in adults. Anesth analg;100:1093-106.

12. Boldt J (2005).Volume therapy in cardiac surgery. Annals of cardiac anesthesia; 8:104-16.

13. Gan TJ et al(2002). Goal-directed Intraoperative Fluid Administration Reduces Length of Hospital Stay after Major Surgery. Anesthesiology ; 97:820–6

14. Callum KG, Gray AJG, Hoile RW et al(1999). Extremes of Age: The 1999 Report of the National Confidential Enquiry into Perioperative Deaths. London: National Confidential Enquiry into Perioperative Deaths.

15. Lowell JA, Schifferdecker C, Driscoll DF et al (1990). Postoperative fluid overload: not a benign problem. Critical Care Medicine; 18: 728–733.