Colloid or Crystalloid: Any Differences in Outcomes?

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INTRODUCTION

The choice of colloid or crystalloid as the optimal intraoperative resuscitation fluid remains unresolved, and disagreement exists over the selection of crystalloid or colloid as the optimal resuscitation fluid.[1,2] There are inherent differences between colloids and crystalloids that contribute to their effects. Colloids have a larger molecular weight, and hence expand the intravascular compartment more effectively.[3,4] Specifically, colloids have been shown to improve oxygen transport, myocardial contractility and cardiac output.[5,6]Arguments in favor of using crystalloids include the observations that they expand the extracellular compartment more effectively with less increase in extravascular pulmonary water as a result of rapid equilibration.[7,8] Crystalloids also minimize the risk of anaphylactoid reactions and cost less than colloids.[9,10] However, crystalloid reduces colloid oncotic pressure and may predispose to pulmonary edema 3 and bowel edema.[11] Tissue edema may also interfere with tissue oxygen exchange and delay in wound healing.[12]

TYPES OF FLUID

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

CRYSTALLOID SOLUTIONS

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

Significant plasma volume expansion requires large volume crystalloid infusion. This causes a significant expansion of the extracellular volume that leads to tissue edema. Large volume crystalloid resuscitation following major burns is associated with significant tissue edema when compared with colloid resuscitation.[13] Theoretically this will result in increasing diffusion distances within tissues and compression of small vessels and capillaries result in compromised end-organ perfusion and oxygenation. Animal studies demonstrate that crystalloid infusion is associated with significant tissue fluid accumulation[14,15] but it is unclear as to whether this is greater than that which occurs following colloid administration.[16,17] Similarly data on whether tissue oxygen extraction is altered by accumulation of interstitial fluid is inconclusive with evidence in support of[14,18] and refuting this proposition.[19] Kimberger et al[20] in a pig hand-sewn colon anastomosis model recently showed that goal directed colloid resuscitation was associated with a greater degree of perioperative increase in tissue oxygen tension and microcirculatory blood flow compared with goal directed crystalloid administration.

Prien and colleagues 11 demonstrated that, in patients undergoing Whipple's procedure, crystalloid

Table 1. Comparison of contents, osmolarity and pH of crystalloid solutions for intravenous administration.

Solution	Osmolarity mOsmol/L	pH	Na^+mmol/L	Cl^-mmol/L	K^+mmol/L	Ca^{2+}mmol/L	Glucose mg/L	HCO_3^- mmol	Lactate mmol/L	Energy Kcal/L
Glucose 5%	252		-	-	-	-	50	-	-	400
Glucose 25%	1260		-	-	-	-	250	-	-	2000
Glucose 50%	2520		-	-	-	-	500	-	-	4000
Sodium Chloride 0.9%	308	5.0	154.0	154.0	-	-	-	-	-	-
Sodium Chloride and Glucose	264		31.0	31.0	-	-	40	-	-	320
Ringer's solution	309		147.0	156.0	4.0	2.2	-	-	-	-
Compound Sodium Lactate *	278		131.0	111.0	5.0	2.0	-	-	29.0	-
Plasmalyte B	298.5	5.5	140	98	5	-	-	50	-	-
Normasol+	280	7.4	140	98	5					

*Compound sodium lactate = Hartmanns' solution or Ringer's Lactate solution.
+Normasol contains acetate 27 mmol/L and gluconate 23 mmol/L

Table 2. Comparison of colloid solutions for intravenous administration.

Solution	Colloid Type	MWn/MWw KDaltons	DS	Na^+mmol/L	Cl^-mmol/L	K^+mmol/L	Ca^{2+}mmol/L	Glucose mg/L
Hespan 6%	Hetastarch	70/450	0.7	150	150	-	-	-
Hextend	Hetastarch	70/450	0.7	143	124	3	5	90
EloHaes 6%	Pentastarch	60/250	0.5	154	154	-	-	-
HAES-steril 6% or 10%	Pentastarch	70/250	0.5	154	154	-	-	-
Pentaspan 10%	Pentastarch	70/250	0.45	154	154			
Voluven	Tetrastarch	60/130	0.4	154	154			
Volulyte	Tetrastarch	60/130	0.4	137	110	4		
Gelofusine (4%)	Succinylated Gelatin	30	-	154	154	-	-	-
Haemaccel (3.5%)	Polygeline	30	-	145	145	5.1	6.25	-
Gentran 40	Dextran 40	40	-	154	154	-	-	-50
Gentran 70	Dextran 70	70	-	154	154	-	-	50
Rheomacrodex	Dextran 40	40	-	154	154	-	-	50
Macrodex	Dextran 70	70	-	154	154	-	-	50

Hextend also contain magnesium 0.9 mmol/L and lactate 28 mmol/L.
Volulyte also contain magnesium 1.5 mmol/L and acetate 34 mmol/L.

resuscitation with LR resulted in a significant increase in the water content of a jejunal specimen compared with intraoperative resuscitation with hetastarch or albumin. Intestinal edema has been associated with impaired gastrointestinal function intolerance for enteral nutrition,[21,22] an increase potential for the development of bacterial translocation, and the development of multiple organ dysfunction syndrome.[23,24]

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

Hypertonic solutions are commonly considered to be irritant to veins because of their high osmolarity and it is recommended that they be given into large veins or centrally although the evidence base for this advice is sparse. A limited study using 7.5% saline/6% dextran 70 failed to demonstrate any vessel damage following brief (2 min) rapid infusion through cephalic vein or femoral artery.[25] However 11.7% saline, which is the minimum effective concentration for use as clinically as a sclerosing agent,[26] has been demonstrated to cause immediate clinical and histological endothelial damage and thrombosis when infused into small veins in animal models.[27] Parenteral nutrition solutions up to 3 times normal osmolarity seems to be readily tolerated by peripheral veins[28] suggesting that the weaker hypertonic solutions (e.g. 1.8% Saline) can safely be administered peripherally.

COLLOID SOLUTIONS

A colloid is a homogeneous non-crystalline substance consisting of large molecules or ultramicroscopic particles of one substance dispersed through a second substance - the particles do not settle and cannot be separated out by ordinary filtering or centrifuging like those of a suspension such as blood. Colloid solutions used in clinical practice for fluid therapy are divided into the semisynthetic colloids (gelatins, dextrans and hydroxyethyl starches) and the naturally occurring human plasma derivatives (human albumin solutions, plasma protein fraction, fresh frozen plasma, and immunoglobulin solution). Most colloid solutions are presented with the colloid molecules dissolved in isotonic saline but isotonic glucose, hypertonic saline and isotonic balanced or "physiological" electrolyte solutions are also used. See Table 2.

Colloid molecular size can be highly variable. The semisynthetic colloids and the various preparations of plasma proteins in solution (e.g. fresh frozen plasma, plasma protein fraction) have a wide distribution of molecular sizes and are described as polydisperse. Human albumin solution contains more than 95% albumin with a uniform molecular size and is described as monodisperse. The size weight relationship is in most cases relatively constant although some colloids of equivalent molecular weight (MW) can have different molecular sizes (e.g. succinylated and urea linked gelatins have similar molecular weights but the succinylated product is physically larger due to increase in negative charge causing a conformational change). Colloid MW can be described as the weight averaged MW (MWw: the number of molecules at each weight multiplied by the particle weight divided by the total weight of all the molecules) or number averaged MW (MWn: the arithmetic mean of all particle MWs). The pattern of weight distribution can also be described by

the ratio of osmotic activity of a colloid solution across membranes with different pore sizes: the COP ratio.[29]

GELATINS

Gelatins are prepared by hydrolysis of bovine collagen. Succinylated gelatin (Gelofusin™) is produced by enzymatic alteration of the basic gelatin peptide and is presented in isotonic saline. Succinylation causes a conformational change that increases molecular size without significantly increasing molecular weight.[30] Urea linked gelatin (polygeline, Haemaccel™) is produced by thermal degradation of the raw material to small peptides (12000 to 15000 Dalton) followed by urea cross-linking to produce polymers of around 35000 Daltons[31] and is presented in an isotonic solution of sodium chloride with 5.1 mmol/L potassium and 6.25 mmol/L calcium.[32] Because of the significant calcium content of Haemaccel™ blood should not be infused through a giving set that has been previously used for this product.

Concerns have been raised about the risks associated with bovine derived gelatin because of the association between new variant Creutzfeld-Jakob disease (CJD) and Bovine Spongiform Encephalitis (BSE). All reported cases implicate bovine derived food products and there are no known cases of transmission involving pharmaceutical gelatin preparations. Most clinicians continue to use bovine gelatin based products; however, given the uncertainties concerning the transmission and behavior of BSE awareness of this issue is important.[33-35]

DEXTRANS

Dextrans are biosynthesized commercially from sucrose by Leuconostoc bacteria using the enzyme dextran sucrase.[36] The high molecular weight dextrans produced are then cleaved by acid hydrolysis and separated by repeated ethanol fractionation into a final product with a restricted molecular weight range. The products of this process are D-glucose polymers joined largely by alpha 1,6 bonds into predominantly linear macromolecules. They are defined by their MWn: Dextran 40 and Dextran 70 having MWns of 40,000 and 70,000 Daltons respectively.[30] Dextrans are polydisperse and clearance is dependant upon molecular weight. Dextran molecules of less than 50-55,000 Daltons are freely filtered at the renal glomerulus and around 70% of an administered dose of Dextran 40 will be excreted into the urine within 24 hours. Larger molecules are excreted through the gut or metabolized by endogenous dextranases in reticuloendothelial cells.[37]

ALBUMIN AND PLASMA PROTEIN FRACTION

The use of human derived colloid has a number of significant disadvantages including high cost and the theoretical risk of transmission of infectious agents such as New Variant Creutsfeld-Jakob disease associated with BSE. A systematic review of human albumin in the critically ill suggested that administration might increase mortality.[38] However this analysis was widely criticized for the heterogeneity of included studies. In most countries use of albumin in the management of hypovolemia is relatively uncommon because the semisynthetic colloids are believed to be at least as effective.

HYDROXYETHYL STARCHES

Hydroxyethyl starches (HES) are synthesized from amylopectin, a branching D-glucose polymer derived from maize or sorghum. Hydroxyethyl substitution by ethylene oxide occurs in the presence of an alkaline catalyst. The majority of substitutions occur at carbon 2 in the glucose ring, with a minority occurring at carbon 3 and 6, and a higher C2/C6 substitution ratio results in slower enzymatic degradation.[39] Hydroxyethylation slows hydrolysis by non-specific *-amylases in the blood; unsubstituted starch molecules are rapidly metabolized. The degree of substitution (DS), expressed as a number between 0 and 1, describes the proportion of substituted to non-substituted glucose moieties and an increased DS confers greater resistant to hydrolysis. The final product is produced by hydrolysis of the substituted starch to the required molecular weight followed by a purification process. Fractionation to produce narrower molecular weight bands is used for some products. The molecular weight profile and degree of substitution define the individual products. HES products can be divided into three classes by their MWw: high MW (450-480 KD), medium MW (around 200 KD) and low LW (70-130 KD). Examples of commercially available starches are 6% high MW hetastarch in saline (Hespan™), 6% high MW hetastarch in balanced electrolyes (Hextend™), medium MW pentastarch in saline (Elo-HAES™, HAES-steril™) and low MW tetrastarch in saline (Voluven) or in balance salt (Volulyte).

PROPERTIES OF COLLOIDS

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

The duration of plasma volume expansion produced by each colloid is governed by the rate of loss of colloid molecules from the circulation and by their metabolism. Rate of loss through the capillary endothelial barrier into the interstitial space and through the renal glomerulus into the urine is determined by molecular size (and therefore weight) and surface charge characteristics. The rate of intra- and extra- vascular metabolism is governed by specific chemical qualities of molecules (e.g. HES C2/C6 ratio and resistance to hydrolysis). The most useful descriptors of magnitude and duration of plasma volume expansion (PVE) are the intravascular half-life and the fraction of administered volume retained within the circulation after a specific time. Ninety minutes after administration of one liter

the gelatins produce a PVE of around 0.2L (equivalent to crystalloid) whereas Dextran and HES preparations produce a PVE of 0.7-0.8 liters.[40]

The predominant effect of colloid solutions on blood rheology (the physics of flow and deformation of matter) is to reduce whole blood viscosity by simple hemodilution thus improving blood flow characteristics.[41] The magnitude of this effect is proportional to the degree of plasma volume expansion and is therefore greater initially for the lower molecular weight (130,000 – 150,000 Dalton) HES and Dextran products that produce a large initial increment in intravascular volume and therefore a larger hemodilution effect. Independent of this dilutional increase in viscosity semisynthetic colloids also influence plasma viscosity and red cell aggregation that contribute to their overall effect on whole blood rheology. The higher molecular weight dextrans and hydroxyethyl starches cause an increase in plasma viscosity and the larger dextrans (e.g. Dextran 70) and gelatins also tend to cause red cell aggregation.[42] These effects are smaller in magnitude than the dilutional increase in whole blood viscosity but investigators are divided as to whether blood flow and tissue oxygenation can be compromised.[42,43] The lower molecular weight dextrans (eg. Dextran 40), starches and human albumin solution tend to cause reduced red blood cell aggregation and plasma viscocity[42,44] and this further enhances dilutional hypoviscosity resulting in increased flow particularly in the venous system.

All of the semisynthetic colloids have been shown to have an effect on hemostasis. This occurs partly as a result of simple hemodilution of clotting factors and partly due to colloid specific effects on components of the hemostatic mechanism. There is also increasing evidence that crystalloid hemodilution can induce a hypercoagulable state but the clinical significance is uncertain,[45,46] The gelatins appear to have the least impact on hemostasis however some abnormalities have been noted in over and above simple hemodilution of clotting factors. Gelatin use has been associated with reduced levels of Von Willebrand factor and factor VIIIc and studies with the thromboelastograph (TEG)[47] and sonoclot[48] technology suggest that clot strength may be reduced after large volume gelatin infusions. However there is little evidence that this results in increased blood loss or adverse bleeding events.[49] HES solutions have varying effects on hemostasis dependent on the molecular weight of the HES molecule.[50] Although conventional clotting indices are unaffected high molecular weight HES products in particular have been reported to produce a coagulopathy and this is thought to be associated with increased blood loss following surgery.[49,51,52] Impaired platelet function, a von Willebrand-like syndrome with reduced vWF and factor VIIIc, and impaired coagulation measured using the TEG have been reported and may explain these clinical findings.[53,54] Medium and low molecular weight HES preparations have been shown to produce similar, but lesser effects compared to the higher molecular weight products and it is believed that the risk of increased blood loss is minimal with these products.[50,55] The Dextrans are associated with more significant hemostatic derangements[56,57] and are effective antithrombotic agents.[58,59] In addition to simple hemodilution of clotting factors, low molecular weight Dextrans increase microvascular flow by platelet disaggregation and have specific effects on several components of the hemostatic system[60] Factor VIIIc and von Willebrands factor (vWF) are reduced, as is Factor VIII activity.[49] Red cell aggregation is also reduced with the lower molecular weight Dextrans. In patients whose hemostatic function is normal prior to infusion a maximum dose of 1.5-2g/kg is often recommended to avoid risk of bleeding complications.

Dextran and HES molecules may also have specific anti-inflammatory effects including reducing post-ischemic leukocyte-endothelial interactions and platelet adhesiveness.[37] In general the effect is stronger for Dextran preparations although Pentastarch (HES pentafraction) is thought to exert more pronounced inhibition of endothelial cell activation and neutrophil adhesion. Pentafraction is also believed to have specific benefits in retaining fluid within the capillaries, probably by physically plugging of endothelial pores, in situations where capillary leak occurs.[61]

Anaphylaxis or anaphylactoid events have been described in association with all of the semisynthetic colloids and albumin. The incidence of severe reactions (life-threatening event e.g. shock, life-threatening smooth muscle spasm, cardiac or respiratory arrest) is probably higher for Gelatins (highest reported incidence <0.35%) and Dextrans (<0.28%) than for albumin (<0.1%) or HES (<0.06%).[41] The advent of Dextran 1 hapten treatment has significantly reduced the risk of dextran related anaphylactic events to <0.0015%.[62] For comparison the rate of serious reactions to Penicillin is of the order of <0.05%. A significant incidence of itch has been noted with HES products by some authors.[63]

CRYSTALLOIDS VS. COLLOIDS

A longstanding controversy exists between crystalloid and colloid enthusiasts relating to the relative merits of the two fluid classes. The arguments center around the increase in edema associated with crystalloid therapy and the known adverse effects (hemostatic impairment, anaphylaxis etc) associated with colloid use. A large number of randomized controlled trials (RCTs) have been conducted to compare colloid and crystalloid fluid therapy in a variety of clinical settings although none have focused on mortality as an endpoint. Three systematic reviews have focused specifically on this issue.[64-66] Meta-analyses from the first two reviews suggested an increase in mortality associated with colloid use however the most recent analysis reported that " Methodologic limitations preclude any evidence-based clinical recommendations" and proposed large carefully designed RCTs to directly address this question. The majority of clinicians use a combination of crystalloid and colloid fluid therapy in the absence

of clear guidance from the available literature. Recent evidence suggests that colloid resuscitation may result in less edema and better quality of recovery in the postoperative period. Specifically, these patients had a lower incidence of nausea and vomiting and severe pain, which could be explained by the lower degree of tissue edema.[67]

PHYSIOLOGICALLY "BALANCED" VS. "UNBALANCED" FLUIDS

Large volume use of 0.9% saline, and of colloids dissolved in isotonic saline, is associated with the development of hyperchloremic metabolic acidosis due to the high chloride load.[51,68,69] Balanced or physiological fluids that contain inorganic ions (calcium, potassium or magnesium), molecular glucose, buffer components such as bicarbonate or lactate and have a lower chloride concentration are not associated with the same disturbance of acid/base physiology.[51,68,69] Recent data suggests that this acidosis may be clinically significant. Patients randomized to balanced solutions when compared with those randomized to saline based fluids had less impairment of hemostasis[46,70] and improved gastric perfusion.[51] Renal function may also be better preserved.[51] Balanced crystalloid solutions have been available for many years (e.g. Hartmann's solution – Ringer's Lactate). Colloid solution in a "balanced" 6% HES in a balanced electrolyte solution (Hextend®) are now widely available in the USA[70,71] and a low molecular weight balanced starch (Volulyte®) is also available in some parts of Europe and Asia.

In summary, the choice of fluid administration in the perioperative period can affect postoperative outcomes. Colloid results in a more effective plasma volume expansion compared to crystalloid and hence

lower volumes are required. Crystalloid is an essential part of perioperative fluid regimen for replenishing insensible and interstitial fluid loss. However, large volumes of crystalloid are associated with gastrointestinal dysfunction and delay bowel recovery. Balanced salt solutions appear to provide better postoperative outcomes than normal saline.

REFERENCES

1. 1. Grocott MP, Mythen MG, Gan TJ: Perioperative fluid management and clinical outcomes in adults. Anesthesia & Analgesia 2005; 100: 1093-106
2. 2. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M: A rational approach to perioperative fluid management. Anesthesiology 2008; 109: 723-40
3. 3. Rackow EC, Falk JL, Fein IA, Siegel JS, Packman MI, Haupt MT, Kaufman BS, Putnam D: Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. Critical Care Medicine 1983; 11: 839-50
4. 4. Shoemaker WC, Schluter M, Hopkins JA, al e: Comparison of the relative effectiveness of colloids and crystalloids in emergency resuscitation. Am J Surg 1981; 142: 73-81
5. 5. Hauser CJ, Shoemaker WC, Turpin I, al e: Oxygen transport responses to colloids and crystalloids in critically ill surgical patients. Surg Gynecol Obstet 1980; 150: 811-16
6. 6. Hankeln K, Radel C, Beez M, al e: Comparison of hydroxyethyl starch and lactated ringer's solution on hemodynamics and oxygen transport of critically ill patients in prospective crossover studies. Crit Care Med 1989; 17: 133-35
7. 7. Tranbaugh RF, Elings VB, Christensen J, Lewis FR: Determinants of pulmonary interstitial fluid accumulation after trauma. Journal of Trauma-Injury Infection & Critical Care 1982; 22: 820-6
8. 8. Gallagher JD, Moore RA, Kerns D, Jose AB, Botros SB, Flicker S, Naidech H, Clark DL: Effects of colloid or crystalloid administration on pulmonary extravascular water in the postoperative period after coronary artery bypass grafting. Anesthesia & Analgesia 1985; 64: 753-8
9. 9. Moss GS, Lowe RJ, Jilek J, Levine HD: Colloid or crystalloid in the resuscitation of hemorrhagic shock: a controlled clinical trial. Surgery 1981; 89: 434-8
10. 10. Lowe RJ, Moss GS, Jilek J, Levine HD: Crystalloid vs colloid in the etiology of pulmonary failure after trauma: a randomized trial in man. Surgery 1977; 81: 676-83
11. 11. Prien T, Backhaus N, Pelster F, Pircher W, Bunte H, Lawin P: Effect of intraoperative fluid administration and colloid osmotic pressure on the formation of intestinal edema during gastrointestinal surgery. Journal of Clinical Anesthesia 1990; 2: 317-23
12. 12. Twigley AJ, Hillman KM: The end of the crystalloid era? A new approach to peri-operative fluid administration. Anaesthesia 1985; 40: 860-71
13. 13. Ahlborg G, Lundberg JM: Splanchnic release of neuropeptide Y during prolonged exercise with and without beta-adrenoceptor blockade in healthy man. Clinical Physiology 1991; 11: 343-51
14. 14. Baum TD, Wang H, Rothschild HR, Gang DL, Fink MP: Mesenteric oxygen metabolism, ileal mucosal hydrogen ion concentration, and tissue edema after crystalloid or colloid resuscitation in porcine endotoxic shock: comparison of Ringer's lactate and 6% hetastarch. Circ Shock 1990; 30: 385-97.
15. 15. Moon PF, Hollyfield-Gilbert MA, Myers TL, Kramer GC: Effects of isotonic crystalloid resuscitation on fluid compartments in hemorrhaged rats. Shock 1994; 2: 355-61.
16. 16. Bressack MA, Morton NS, Hortop J: Group B streptococcal sepsis in the piglet: effects of fluid therapy on venous return, organ edema, and organ blood flow. Circ Res 1987; 61: 659-69.
17. 17. Rackow EC, Astiz ME, Schumer W, Weil MH: Lung and muscle water after crystalloid and colloid infusion in septic rats: effect on oxygen delivery and metabolism. J Lab Clin Med 1989; 113: 184-9.
18. 18. Ostgaard G, Reed RK: Interstitial fluid accumulation does not influence oxygen uptake in the rabbit small intestine. Acta Anaesthesiol Scand 1995; 39: 167-73.
19. 19. Gotohda N, Iwagaki H, Itano S, Horiki S, Fujiwara T, Saito S, Hizuta A, Isozaki H, Takakura N, Terada N, Tanaka N: Can POSSUM, a scoring system for perioperative surgical risk, predict postoperative clinical course? Acta Medica Okayama 1998; 52: 325-9
20. 20. Kimberger O, Arnberger M, Brandt S, Plock J, Sigurdsson GH, Kurz A, Hiltebrand L: Goal-directed colloid administration improves the microcirculation of healthy and perianastomotic colon. Anesthesiology 2009; 110: 496-504
21. 21. Moss GS: Plasma albumin and postoperative ileus. Surg Forum 1967; 18: 333-6
22. 22. Falk JL: Fluid resuscitation and colloid-crystalloid controversy: New thoughts on an old debate. Crit Care Med 1991; 19: 451-53
23. 23. Baker JW, Deitch ED, Ma LM, al e: Hemorrhagic shock induces baterial translocation from the gut. J Trauma 1988; 28: 896-06
24. 24. Wilmore DW, Smith RJ, O'Dwyer ST, al e: The gut - a central organ following surgical stress. Surgery 1988; 104: 917-23
25. 25. Hands R, Holcroft JW, Perron PR, Kramer GC: Comparison of peripheral and central infusions of 7.5% NaCl/6% dextran 70. Surgery 1988; 103: 684-9.
26. 26. Sadick NS: Sclerotherapy of varicose and telangiectatic leg veins. Minimal sclerosant concentration of hypertonic saline and its relationship to vessel diameter. J Dermatol Surg Oncol 1991; 17: 65-70.
27. 27. Goldman MP: A comparison of sclerosing agents. Clinical and histologic effects of intravascular sodium morrhuate, ethanolamine oleate, hypertonic saline (11.7%), and sclerodex in the dorsal rabbit ear vein. J Dermatol Surg Oncol 1991; 17: 354-62.
28. 28. Bodoky A, Zbinden A, Muller J, Leutenegger A: [Peripheral venous tolerance of hyperosmolar infusion solutions]. Helv Chir Acta 1980; 47: 151-6.
29. 29. Mythen MG, Salmon JB, Webb AR: The rational administration of colloids. Blood Reviews 1993; 7: 223-8
30. 30. Salmon JB, Mythen MG: Pharmacology and physiology of colloids. Blood Reviews 1993; 7: 114-20
31. 31. Mishler JMt: Synthetic plasma volume expanders--their pharmacology, safety and clinical efficacy. Clin Haematol 1984; 13: 75-92.
32. 32. Saddler JM, Horsey PJ: The new generation gelatins. A review of their history, manufacture and properties. Anaesthesia 1987; 42: 998-1004

33. 33. Atherton P, Davies MW: Gelatin solutions. Anaesthesia 1996; 51: 989.

34. 34. Bedforth NM, Hardman JG: Mad colloid disease? Anaesthesia 1997; 52: 389-90.

35. 35. Marwick C: BSE sets agenda for imported gelatin. Jama 1997; 277: 1659-60.

36. 36. Mishler JM: Pharmacological effects produced by the acute and chronic administration of hydroxyethyl starch. J Clin Apheresis 1984; 2: 52-62.

37. 37. Haljamae H DM, Walentin F.: Artificial colloids in clinical practise: pros and cons. Bailliere's Clinical Anaesthesiology 1997; 11: 49-79

38. 38. Anonymous: Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet 2000; 355: 1295-302

39. 39. Treib J, Haass A, Pindur G, Seyfert UT, Treib W, Grauer MT, Jung F, Wenzel E, Schimrigk K: HES 200/0.5 is not HES 200/0.5. Influence of the C2/C6 hydroxyethylation ratio of hydroxyethyl starch (HES) on hemorheology, coagulation and elimination kinetics. Thrombosis & Haemostasis 1995; 74: 1452-6

40. 40. Lamke LO, Liljedahl SO: Plasma volume changes after infusion of various plasma expanders. Resuscitation 1976; 5: 93-102

41. 41. Audibert G, Donner M, Lefevre JC, Stoltz JF, Laxenaire MC: Rheologic effects of plasma substitutes used for preoperative hemodilution. Anesthesia & Analgesia 1994; 78: 740-5

42. 42. Freyburger G, Dubreuil M, Boisseau MR, Janvier G: Rheological properties of commonly used plasma substitutes during preoperative normovolaemic acute haemodilution. British Journal of Anaesthesia 1996; 76: 519-25

43. 43. Krieter H, Bruckner UB, Kefalianakis F, Messmer K: Does colloid-induced plasma hyperviscosity in haemodilution jeopardize perfusion and oxygenation of vital organs? Acta Anaesthesiol Scand 1995; 39: 236-44.

44. 44. Treib J, Haass A, Pindur G: Hetastarch Coagulopathy. Journal of Neurosurgery 1996; 85: 367-8; discussion 368

45. 45. Ruttmann TG, James MF, Viljoen JF: Haemodilution induces a hypercoagulable state. British Journal of Anaesthesia 1996; 76: 412-4

46. 46. Martin G, Bennett-Guerrero E, Wakeling H, Mythen MG, el-Moalem H, Robertson K, Kucmeroski D, Gan TJ: A prospective, randomized comparison of thromboelastographic coagulation profile in patients receiving lactated Ringer's solution, 6% hetastarch in a balanced-saline vehicle, or 6% hetastarch in saline during major surgery. Journal of Cardiothoracic & Vascular Anesthesia 2002; 16: 441-6

47. 47. Mardel SN, Saunders FM, Allen H, Menezes G, Edwards CM, Ollerenshaw L, Baddeley D, Kennedy A, Ibbotson RM: Reduced quality of clot formation with gelatin-based plasma substitutes. Br J Anaesth 1998; 80: 204-7.

48. 48. Brazil EV, Coats TJ: Sonoclot coagulation analysis of in-vitro haemodilution with resuscitation solutions. J R Soc Med 2000; 93: 507-10.

49. 49. de Jonge E, Levi M: Effects of different plasma substitutes on blood coagulation: a comparative review. Crit Care Med 2001; 29: 1261-7.

50. 50. Strauss RG, Pennell BJ, Stump DC: A randomized, blinded trial comparing the hemostatic effects of pentastarch versus hetastarch. Transfusion 2002; 42: 27-36.

51. 51. Wilkes NJ, Woolf R, Mutch M, Mallett SV, Peachey T, Stephens R, Mythen MG: The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. Anesthesia & Analgesia 2001; 93: 811-6

52. 52. Knutson JE, Deering JA, Hall FW, Nuttall GA, Schroeder DR, White RD, Mullany CJ: Does intraoperative hetastarch administration increase blood loss and transfusion requirements after cardiac surgery? Anesthesia & Analgesia 2000; 90: 801-7

53. 53. Tobias MD, Wambold D, Pilla MA, Greer F: Differential effects of serial hemodilution with hydroxyethyl starch, albumin, and 0.9% saline on whole blood coagulation. J Clin Anesth 1998; 10: 366-71.

54. 54. Claes Y, Van Hemelrijck J, Van Gerven M, Arnout J, Vermylen J, Weidler B, Van Aken H: Influence of hydroxyethyl starch on coagulation in patients during the perioperative period. Anesth Analg 1992; 75: 24-30.

55. 55. Langeron O, Doelberg M, Ang ET, Bonnet F, Capdevila X, Coriat P: Voluven, a lower substituted novel hydroxyethyl starch (HES 130/0.4), causes fewer effects on coagulation in major orthopedic surgery than HES 200/0.5. Anesthesia & Analgesia 2001; 92: 855-62

56. 56. Petroianu GA, Liu J, Maleck WH, Mattinger C, Bergler WF: The effect of In vitro hemodilution with gelatin, dextran, hydroxyethyl starch, or Ringer's solution on Thrombelastograph. Anesth Analg 2000; 90: 795-800.

57. 57. Mortier E, Ongenae M, De Baerdemaeker L, Herregods L, Den Blauwen N, Van Aken J, Rolly G: In vitro evaluation of the effect of profound haemodilution with hydroxyethyl starch 6%, modified fluid gelatin 4% and dextran 40 10% on coagulation profile measured by thromboelastography. Anaesthesia 1997; 52: 1061-4

58. 58. Kline A, Hughes LE, Campbell H, Williams A, Zlosnick J, Leach KG: Dextran 70 in prophylaxis of thromboembolic disease after surgery: a clinically oriented randomized double-blind trial. Br Med J 1975; 2: 109-12.

59. 59. Clagett GP, Reisch JS: Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. Ann Surg 1988; 208: 227-40.

60. 60. Bergman A, Andreen M, Blomback M: Plasma substitution with 3% dextran-60 in orthopaedic surgery: influence on plasma colloid osmotic pressure, coagulation parameters, immunoglobulins and other plasma constituents. Acta Anaesthesiologica Scandinavica 1990; 34: 21-9

61. 61. Webb AR, Moss RF, Tighe D, Mythen MG, al-Saady N, Joseph AE, Bennett ED: A narrow range, medium molecular weight pentastarch reduces structural organ damage in a hyperdynamic porcine model of sepsis. Intensive Care Medicine 1992; 18: 348-55

62. 62. Ljungstrom KG: Safety of dextran in relation to other colloids--ten years experience with hapten inhibition. Infusionsther Transfusionsmed 1993; 20: 206-10.

63. 63. Wheeler DW, van Heerden N: Itching after use of starch solutions [letter]. British Journal of Anaesthesia 1999; 83: 973-4

64. 64. Velanovich V: Crystalloid versus colloid fluid resuscitation: a meta-analysis of mortality. Surgery 1989; 105: 65-71

65. 65. Schierhout G, Roberts I: Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. Bmj 1998; 316: 961-4.

66. 66. Choi PT, Yip G, Quinonez LG, Cook DJ: Crystalloids vs. colloids in fluid resuscitation: a systematic review. Critical Care Medicine 1999; 27: 200-10

67. 67. Moretti E, Robertson KM, El-Moalem H, Gan TJ: Intraoperative colloid administration reduces postoperative nausea and vomiting and improves postoperative outcomes compared to crystalloid administration. Anesth Analg 2003; 96: 611-7

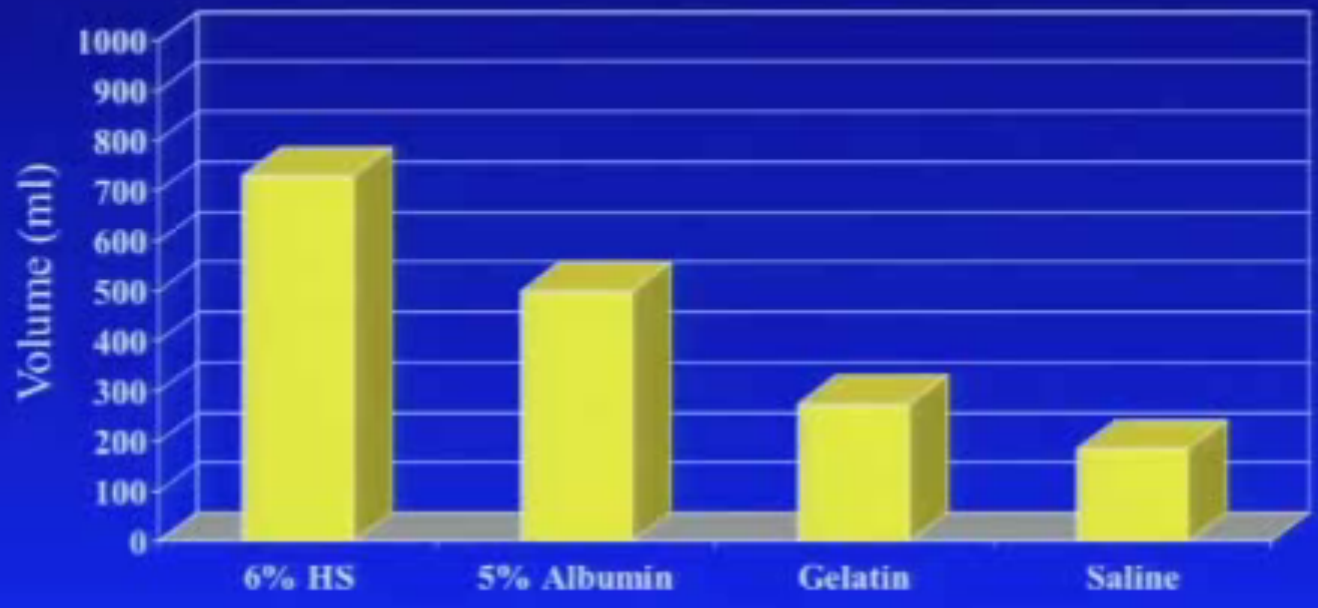
68. 68. McFarlane C, Lee A: A comparison of Plasmalyte 148 and 0.9% saline for intra-operative fluid replacement. Anaesthesia 1994; 49: 779-81

69. 69. Scheingraber S, Rehm M, Sehmisch C, Finsterer U: Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 1999; 90: 1265-70.

70. 70. Gan TJ, Bennett-Guerrero E, Phillips-Bute B, Wakeling H, Moskowitz DM, Olufolabi Y, Konstadt SN, Bradford C, Glass PS, Machin SJ, Mythen MG: Hextend, a physiologically balanced plasma expander for large volume use in major surgery: a randomized phase III clinical trial. Hextend Study Group. Anesthesia & Analgesia 1999; 88: 992-8

71. 71. Wilkes NJ, Woolf RL, Powanda MC, Gan TJ, Machin SJ, Webb A, Mutch M, Bennett-Guerrero E, Mythen M: Hydroxyethyl starch in balanced electrolyte solution (Hextend)--pharmacokinetic and pharmacodynamic profiles in healthy volunteers. Anesth Analg 2002; 94: 538-44.

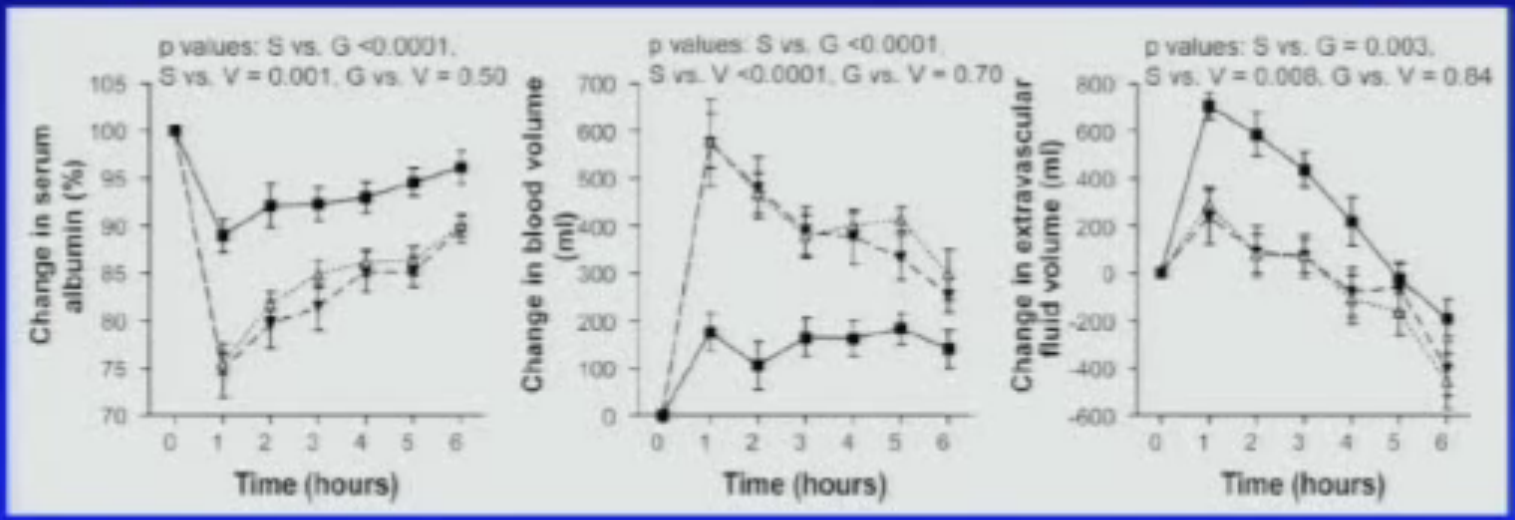
Plasma Volume Expansion Effect 90 min After Fluid Administration



Lamke & Liljedahl Resuscitation 1976;5:93-102

Effect of volume loading with 1 liter intravenous infusions of 0.9% saline, 4% succinylated gelatine (Gelofusine) and 6% hydroxyethyl starch (Voluven) on blood volume and endocrine responses: A randomized, three-way crossover study in healthy volunteers

Dileep N. Lobo, DM, FRCS; Zeno Stanga, MD; Mark M. Aloysius, MRCS; Catherine Wicks, BMedSci, BM, BS; Quentin M. Nunes, MRCS; Katharine L. Ingram, FRCA; Lorenz Risch, MD, MPH; Simon P. Allison, MD, FRCP



Saline (S)
Gelofusine® (G)
Voluven® (V)

Lobo DN et al. Crit Care Med 2010; 38:464–470

Characteristics of Starches

Concentration

- High 10% Hyperoncotic
- Low 6% Iso-osmolar

Degree of Substitution

- High 0.6-0.7
- Medium 0.45-0.6
- Low ≤ 0.4

C2:C6 ratio

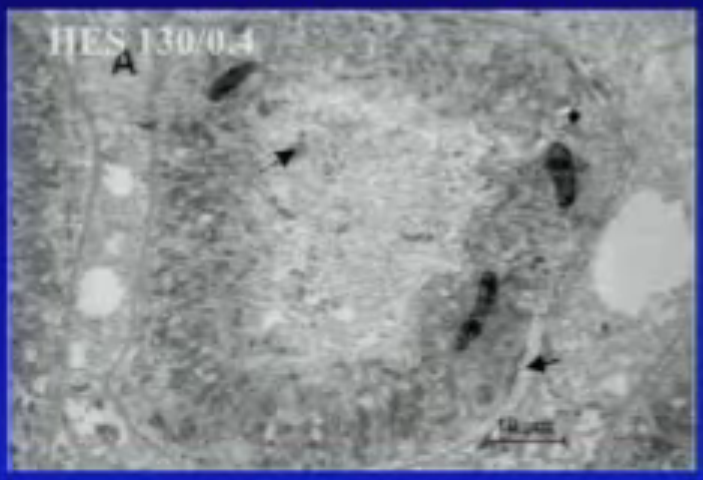
- High > 8
- Low < 8

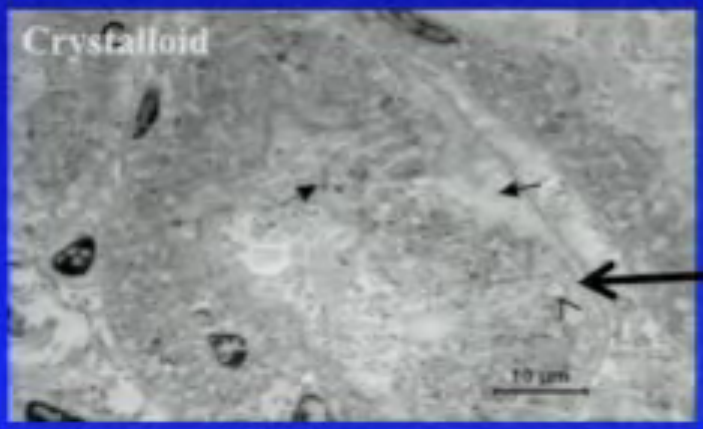
Pharmacology of Starch

Classification	Molecular Weight (kDal)	Degree of Substitution	Examples
High MW	450-480	0.7	Hespan™ Hextend™
Medium MW	200-280	0.5	Elo-HAES™ HAES-steril™ Pentaspan™
Low MW	70-130	0.4	Voluven™ Volulyte™


Renal Adverse Events
Renal Dys-function
Renal Replace-ment Therapy
ICU Death
Day 28 Death
% Incidence (95% CI)
0
5
10
15
20
25
30
35
40
45
50
55
60
P<0.0001
P<0.001
P<0.0001
P<0.067
P<0.030
Frédérique Schortgen et al. ICM 2008
Crystalloids Only
Hypooncotic Colloids
Artificial Hyperoncotic Colloids
Hyperoncotic Albumin

Renal Tubular Injury Scores





Dissociation of epithelium from basal lamina

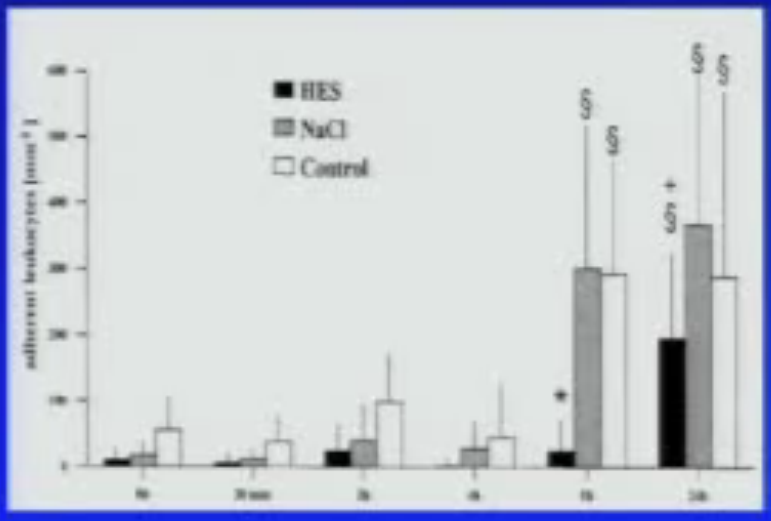
Vacuolar cell degeneration

Edematous tubular epithelial cell

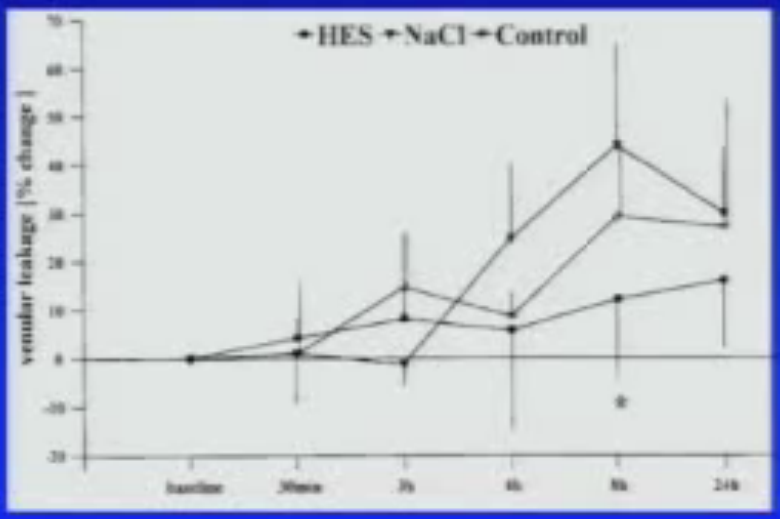
Hydroxyethyl Starch (130 kD), but Not Crystalloid Volume Support, Improves Microcirculation during Normotensive Endotoxemia

Johannes N. Hoffmann, M.D., Brigitte Vollmar, M.D.,† Matthias W. Laschke, M.D.,‡ Dietrich Inthorn, M.D.,§ Friedrich W. Schildberg, M.D.,§ Michael D. Menger, M.D.†*

Adhesion Leukocytes

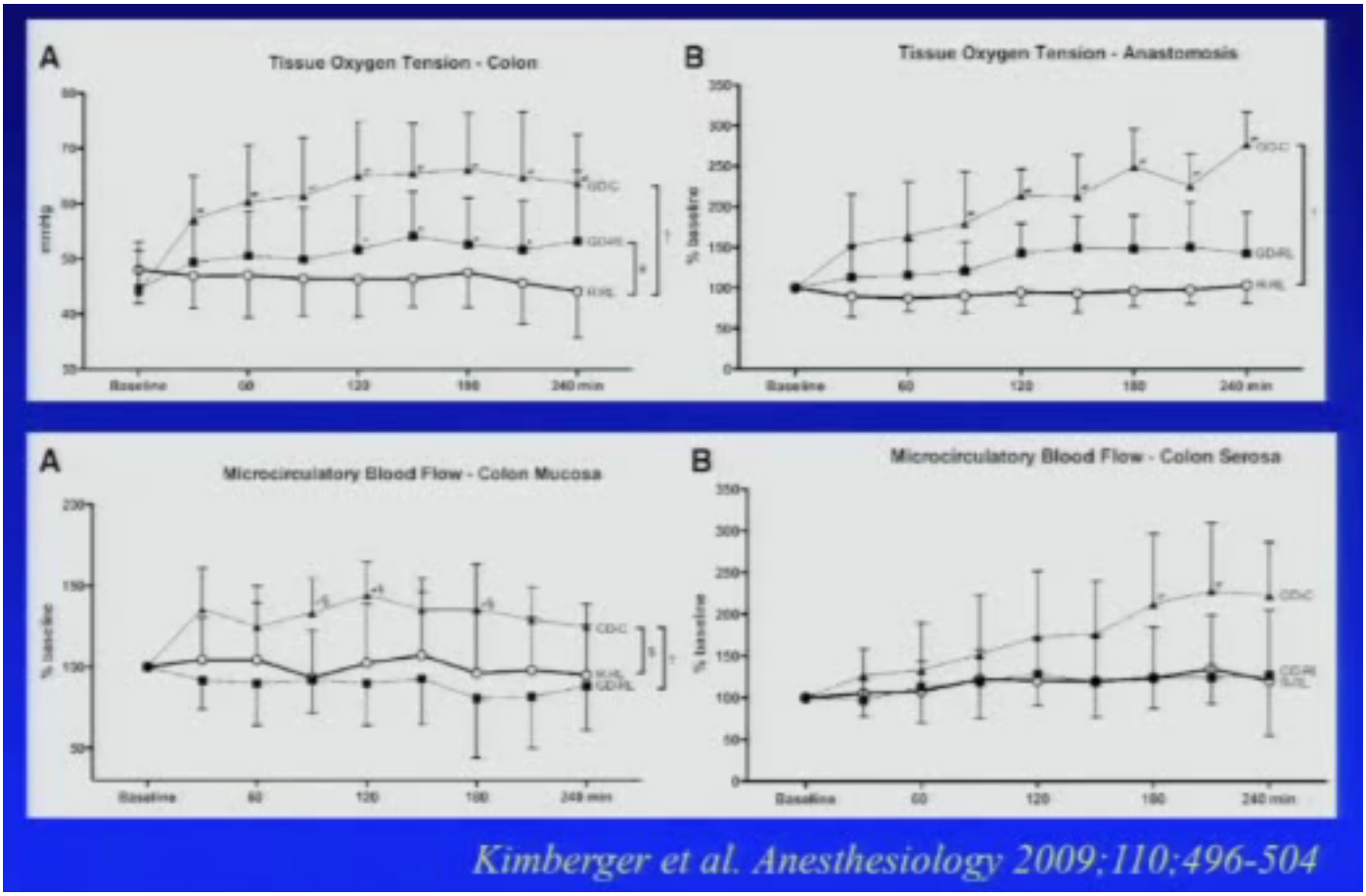


Venular Leakage

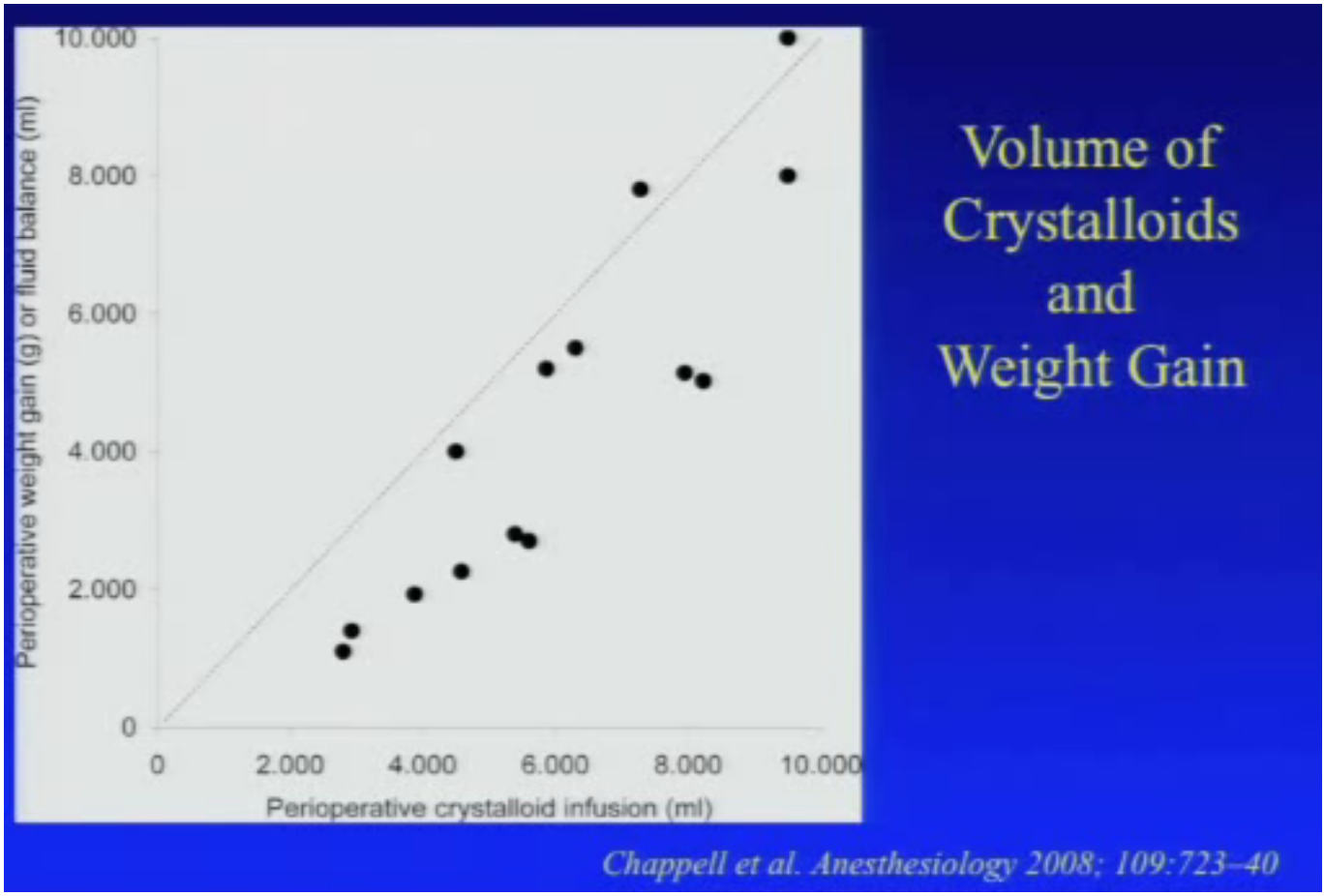


Hoffmann JN et al. Anesthesiology 2002;97 ;460-70

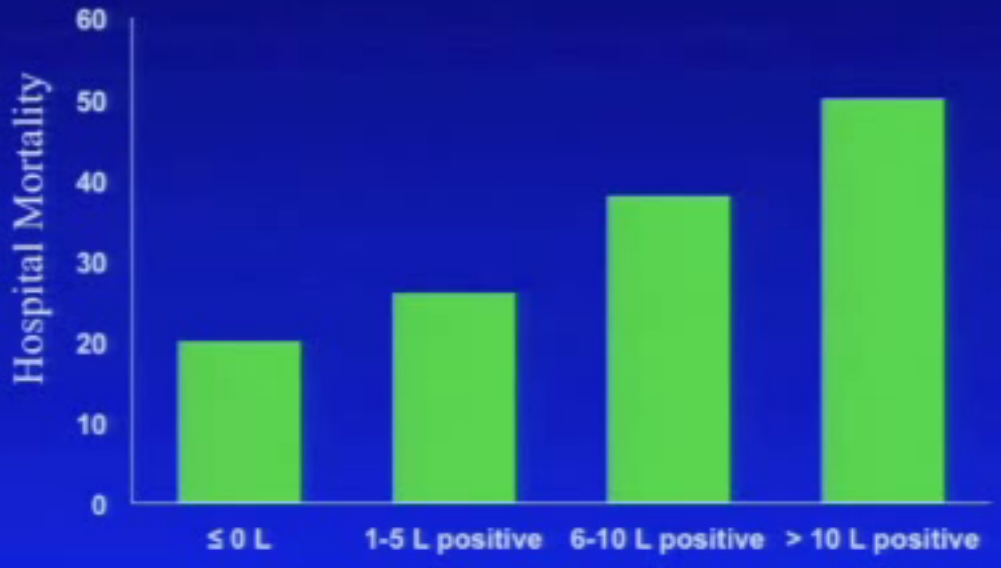
	LR	Normasol	Dextrose LR	0.9% Saline	Dextrose Saline
Na^+	130	140	130	154	77
K^+	4	5	4		
Mg^{2+}		3			
Ca^{2+}	3		3		
Acetate		27			
Cl^-	109	98	109	154	77
Lact	28		28		
Gluconate		23			
pH	6.6	7.4	4.9	5.6	4.3
mOsm	273	280	525	308	560



Kimberger et al. Anesthesiology 2009;110;496-504


Volume of Crystalloids and Weight Gain
Perioperative weight gain (g) or fluid balance (ml)
10.000
8.000
6.000
4.000
2.000
0
0
2.000
4.000
6.000
8.000
10.000
Perioperative crystalloid infusion (ml)
Chappell et al. Anesthesiology 2008; 109:723–40

Fluid Balance and Outcomes



Rosenberg AL, et al. J Intensive Care Med. 2009;24:35-46.