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 accumulation14,15 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 of14,18 and refuting this proposition.19 Kimberger et al20 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>
<thead>
<tr>
<th>Solution</th>
<th>Osmolarity mOsmol/L</th>
<th>pH</th>
<th>Na⁺ mmol/L</th>
<th>Cl⁻ mmol/L</th>
<th>K⁺ mmol/L</th>
<th>Ca²⁺ mmol/L</th>
<th>Glucose mg/L</th>
<th>HCO₃⁻ mmol</th>
<th>Lactate mmol/L</th>
<th>Energy Kcal/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose 5%</td>
<td>252</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50</td>
<td></td>
<td></td>
<td>400</td>
</tr>
<tr>
<td>Glucose 25%</td>
<td>1260</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>250</td>
<td></td>
<td></td>
<td>2000</td>
</tr>
<tr>
<td>Glucose 50%</td>
<td>2520</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>500</td>
<td></td>
<td></td>
<td>4000</td>
</tr>
<tr>
<td>Sodium Chloride 0.9%</td>
<td>308</td>
<td>5.0</td>
<td>154.0</td>
<td>154.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Chloride and Glucose</td>
<td>264</td>
<td>31.0</td>
<td>31.0</td>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td></td>
<td></td>
<td>320</td>
</tr>
<tr>
<td>Ringer’s solution</td>
<td>309</td>
<td>147.0</td>
<td>156.0</td>
<td>4.0</td>
<td>2.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound Sodium Lactate *</td>
<td>278</td>
<td>131.0</td>
<td>111.0</td>
<td>5.0</td>
<td>2.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>29.0</td>
</tr>
<tr>
<td>Plasmalyte B</td>
<td>298.5</td>
<td>5.5</td>
<td>140</td>
<td>98</td>
<td>5</td>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normasol+</td>
<td>280</td>
<td>7.4</td>
<td>140</td>
<td>98</td>
<td>5</td>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Compound sodium lactate = Hartmanns’ solution or Ringer’s Lactate solution. +Normasol contains acetate 27 mmol/L and gluconate 23 mmol/L.
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. However 11.7% saline, which is the minimum effective concentration for use as clinically as a sclerosing agent, has been demonstrated to cause immediate clinical and histological endothelial damage and thrombosis when infused into small veins in animal models. Parenteral nutrition solutions up to 3 times normal osmolarity seems to be readily tolerated by peripheral veins suggesting that the weaker hypertonic solutions (e.g. 1.8% Saline) can safely be administered peripherally.

**COLLOID SOLUTIONS**

Acolloid 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).

### Table 2. Comparison of colloid solutions for intravenous administration.

<table>
<thead>
<tr>
<th>Solution</th>
<th>Colloid Type</th>
<th>MWn/MWw</th>
<th>DS</th>
<th>Na⁺mmol/L</th>
<th>Cl⁻mmol/L</th>
<th>K⁺mmol/L</th>
<th>Ca²⁺mmol/L</th>
<th>Glucose mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hespan 6%</td>
<td>Hetastarch</td>
<td>70/450</td>
<td>0.7</td>
<td>150</td>
<td>150</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hextend</td>
<td>Hetastarch</td>
<td>70/450</td>
<td>0.7</td>
<td>143</td>
<td>124</td>
<td>3</td>
<td>5</td>
<td>90</td>
</tr>
<tr>
<td>EloHaes 6%</td>
<td>Pentastarch</td>
<td>60/250</td>
<td>0.5</td>
<td>154</td>
<td>154</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HAES-steril 6%</td>
<td>Pentastarch</td>
<td>70/250</td>
<td>0.5</td>
<td>154</td>
<td>154</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pentaspan 10%</td>
<td>Pentastarch</td>
<td>70/250</td>
<td>0.45</td>
<td>154</td>
<td>154</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Voluven</td>
<td>Tetrastarch</td>
<td>60/130</td>
<td>0.4</td>
<td>154</td>
<td>154</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Volulyte</td>
<td>Tetrastarch</td>
<td>60/130</td>
<td>0.4</td>
<td>137</td>
<td>110</td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gelofusine (4%)</td>
<td>Succinylated Gelatin</td>
<td>30</td>
<td>-</td>
<td>154</td>
<td>154</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Haemaccel (3.5%)</td>
<td>Polygeline</td>
<td>30</td>
<td>-</td>
<td>145</td>
<td>145</td>
<td>5.1</td>
<td>6.25</td>
<td>-</td>
</tr>
<tr>
<td>Gentran 40</td>
<td>Dextran 40</td>
<td>40</td>
<td>-</td>
<td>154</td>
<td>154</td>
<td>-</td>
<td>-</td>
<td>-50</td>
</tr>
<tr>
<td>Gentran 70</td>
<td>Dextran 70</td>
<td>70</td>
<td>-</td>
<td>154</td>
<td>154</td>
<td>-</td>
<td>-</td>
<td>50</td>
</tr>
<tr>
<td>Rheomacrodex</td>
<td>Dextran 40</td>
<td>40</td>
<td>-</td>
<td>154</td>
<td>154</td>
<td>-</td>
<td>-</td>
<td>50</td>
</tr>
<tr>
<td>Macrodex</td>
<td>Dextran 70</td>
<td>70</td>
<td>-</td>
<td>154</td>
<td>154</td>
<td>-</td>
<td>-</td>
<td>50</td>
</tr>
</tbody>
</table>

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.
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 Daltons) followed by urea cross-linking to produce polymers of around 35000 Daltons 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.27

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 Creutzfeld-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 Hydroxyethyltion 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-HAEST™, HAES-stereif™) and low MW tetra starch 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 hemostasis, 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.\textsuperscript{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.\textsuperscript{31} 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 \textendash 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.\textsuperscript{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.\textsuperscript{42,43} The lower molecular weight dextrans (e.g. Dextran 40), starches and human albumin solution tend to cause reduced red blood cell aggregation and plasma viscosity\textsuperscript{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.\textsuperscript{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\textsuperscript{37} and studies with the thromboelastograph (TEG)\textsuperscript{47} and sonoclot 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.\textsuperscript{48} HES solutions have varying effects on hemostasis dependent on the molecular weight of the HES molecule.\textsuperscript{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.\textsuperscript{31,52} 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.\textsuperscript{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.\textsuperscript{50,55} The Dextrans are associated with more significant hemostatic derangements\textsuperscript{56,57} and are effective antithrombotic agents.\textsuperscript{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\textsuperscript{60} Factor VIIIc and von Willebrands factor (vWF) are reduced, as is Factor VIII activity.\textsuperscript{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.\textsuperscript{52} In general the effect is stronger for Dextran preparations although Pentastarch (HES pentafracton) is thought to exert more pronounced inhibition of endothelial cell activation and neutrophil adhesion. Pentafracton 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.\textsuperscript{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%).\textsuperscript{41} The advent of Dextran 1 hapten treatment has significantly reduced the risk of dextran related anaphylactic events to <0.0015%.\textsuperscript{52} 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.\textsuperscript{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.\textsuperscript{54,66} 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.71,68,69 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 hemostasis46,70 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 USA70,21 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

27. 27. Goldman MP: A comparison of sclerosing agents. Clinical and peripheral infusions of 7.5% NaCl/6% dextran 70. Surgery 1988; 104: 917-23