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Review Article

Choice of fluid type: physiological concepts and perioperative indications

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Abstract

The consensus that i.v. resuscitation fluids should be considered as drugs with specific dose recommendations, contraindications, and side-effects has led to an increased attention for the choice of fluid during perioperative care. In particular, the debate concerning possible adverse effects of unbalanced fluids and hydroxyethyl starches resulted in a re-evaluation of the roles of different fluid types in the perioperative setting. This review provides a concise overview of the current knowledge regarding the efficacy and safety of distinct fluid types for perioperative use. First, basic physiological aspects and possible side-effects are explained. Second, we focus on considerations regarding fluid choice for specific perioperative indications based on an analysis of available randomized controlled trials.

Keywords: colloids; fluid therapy; surgical procedures

I.V. fluid administration to maintain tissue perfusion and electrolyte concentrations or to infuse drugs is a daily routine during anaesthesia and surgery. I.V. fluids are increasingly considered as drugs with dose recommendations, indications, contraindications, and side-effects.[1–3] This has resulted in new approaches to avoid unnecessary preoperative fasting and fluid-related morbidity, and the institution of goal-directed fluid therapy to rationalize the use of fluids in the perioperative period.[4,5] In parallel, vigorous debate developed regarding the choice of fluid type, mainly focusing on the importance of avoiding hyperchloraemic metabolic acidosis induced by unbalanced fluids and the unfavourable association of hydroxyethyl starches (HESs) with haemostasis and renal function.

However, the scientific evidence to guide fluid choice and dosing in the perioperative setting is limited, and most guidelines refer to physiological experiments rather than comparative clinical trials. Moreover, data from septic and critically ill patients are translated to the surgical patient without a clear rationale, irrespective of the differences in inflammatory state between these distinct populations. This review is restricted to the use of different fluid types in the perioperative setting and their impact on basic physiology, including microvascular perfusion, glycocalyx integrity, colloid osmotic pressure, and haemostasis. Additionally, we summarize the considerations for choosing a fluid for specific surgical indications, including a semi-structured analysis of the available studies that focus on fluid type and their association with clinically relevant outcomes.

Types of fluids

Composition

The first types of physiological fluids were developed in the 19th century, including a fluid developed by Ringer[6] to mimic blood plasma for *ex vivo* experiments with frog hearts. In 1932, Hartmann and Senn[7] added the buffer lactate to Ringer's

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Table 1 Overview of crystalloid and colloid fluids commonly used in the perioperative setting. Electrolyte concentrations, osmolarity, and pH may be subject to small differences with other reports. HE, hydroxylethyl; HES, hydroxylethyl starch

	Main components	Na^+ (mmol litre^{-1})	Cl^- (mmol litre^{-1})	K^+ (mmol litre^{-1})	Osmolarity (mOsm litre^{-1})	pH
Crystalloids						
Normal saline (0.9% NaCl)	Na^+, Cl^-	154	154	0	308	4.5–7.0
Ringer's lactate	Na^+, Cl^-, K^+, lactate	130	109	4	273	6.0–7.5
Ringer's acetate	Na^+, Cl^-, K^+, acetate	130	112	5	276	6.0–8.0
Plasma-Lyte 148	Na^+, Cl^-, K^+, acetate	140	98	5	294	6.5–8.0
Dextrose 5%	Dextrose	0	0	0	278	3.5–5.5
Colloids						
HES 6%						
670/0.75	Na^+, Cl^-, poly(O-2-HE) starch (hetastarch)	154	154	0	308	3.5–7.0
200/0.50	Na^+, Cl^-, poly(O-2-HE) starch (pentastarch)	154	154	0	326	5.0
130/0.40	Na^+, Cl^-, poly(O-2-HE) starch (Voluven)	154	154	0	308	4.0–5.5
Gelatine	Na^+, Cl^-, gelatine	154	120	0	274	7.1–7.7
Albumin 5%	Na^+, Cl^-, albumin	130–160	130–160	<2	309	6.4–7.4
HyperHAES	Na^+, Cl^-, poly(O-2-HE) starch	1232	1232	0	2464	3.5–6.0
Balanced HES 6%					287	5.7–6.5
670/0.75	Na^+, Cl^-, poly(O-2-HE) starch, lactate (Hextend)	143	124	3	308	5.9
130/0.42	Na^+, Cl^-, poly(O-2-HE) starch, acetate (Tetraspan)	140	118	4	297	5.6–6.4
130/0.42	Na^+, Cl^-, poly(O-2-HE) starch, acetate (Volulyte)	137	110	4	287	5.7–6.5

solution, and created the first balanced crystalloid. In parallel, Jacob Hamburger developed a normal saline solution.[8]

The use of colloids became more common with the infusion of albumin in trauma victims during World War II, followed by the development of artificial colloidal solutions containing dextran, gelatine, or HES. Table 1 gives an overview of commonly used fluids in the perioperative setting with their main components, osmolarity, and pH range. Unbalanced crystalloids (normal saline) and colloids (hetastarch, pentastarch, Voluven, Gelofusine, human albumin 5%, and HyperHAES) contain higher chloride concentrations, whilst in balanced solutions (Ringer's lactate/acetate, Plasma-Lyte 148, Hextend, Tetraspan, Gelaspan, and Volulyte) chloride concentrations are partially replaced with alternative anions and contain more potassium compared to unbalanced solutions. Gelatine- and albumin-containing colloids are commonly used alternatives for HES, especially as the use of HES was abandoned in specific patient populations. Gelatine and albumin are considered to be safe for surgical patients, but the lack of large comparative studies prohibits an extensive analysis of this colloid in view of perioperative care.

Side-effects

Infusion solutions for fluid therapy may have side-effects and are contraindicated in specific populations. All solutions are, therefore, registered as pharmaceutical products by local authorities, the US Food and Drug Administration, and the European Medicines Agency. Whilst large volumes of crystalloid and colloid solutions can lead to hypervolaemia, most solutions can also cause an imbalance in electrolytes, including hyponatraemia, hyperchloraemia, hyperkalaemia, and hypocalcaemia.[5,9] The volume load and electrolyte disturbance can be of particular impact in severe renal, cardiac, or hepatic disease.[10] Here, we describe current knowledge on hyperchloraemia and hyperkalaemia as side-effects of infusion fluids, and provide a concise overview of the association of HES with renal function and haemostatic abnormalities.

Normal saline and hyperchloraemic acidosis

Normal saline (0.9%) contains supraphysiological concentrations of sodium (154 mmol litre^{-1}) and chloride (154 mmol litre^{-1}). Excessive and long-term administration of saline can, therefore, lead to hyperchloraemic metabolic acidosis when chloride concentrations exceed the serum concentration (100–110 mmol litre^{-1}).[4] In a systematic review and meta-analysis, it was shown that resuscitation with high-chloride fluids (chloride concentration >111 mmol litre^{-1}) is associated with a higher risk of acute kidney injury [AKI; relative risk (RR) 1.64, 95% confidence interval (CI) 1.27–2.13; $P<0.001$] and hyperchloraemia (RR 2.87, 95% CI 1.95–4.21; $P<0.001$), whilst mortality was not affected.[11] A limitation of this meta-analysis is the lack of data regarding the volume of crystalloids administered during the perioperative period.[11] A propensity-matched comparison of patients with or without acute postoperative hyperchloraemia (>110 mmol litre^{-1}) showed that hyperchloraemia was an independent predictor of 30-day mortality [odds ratio (OR) 2.05; 95% CI 1.62–2.59].[12] Moreover, patients with subarachnoid haemorrhage and postoperative AKI had a three times higher increase in the serum chloride concentration than patients without AKI.[13] In open abdominal surgery, perioperative balanced crystalloid resuscitation was associated with fewer complications (OR 0.79; 95% CI 0.66–0.97) compared to normal saline in a propensity-matched cohort.[14]

In children undergoing major surgery, the increase in plasma chloride concentration was higher in the normal saline group compared to a balanced crystalloid.[15] However, when large volumes were involved (>46.7 ml kg^{-1}), both crystalloids resulted in comparable elevations of plasma chloride concentration without affecting the outcome.[15] In the

0.9% Saline vs Plasma-Lyte 148 (PL-148) for ICU fluid Therapy (SPLIT) trial, normal saline was compared to a Plasma-Lyte 148 (chloride concentration: 98 mmol litre^{-1}) in critically ill patients admitted to the intensive-care unit (ICU), more than 70% of which were postoperative patients.[16] Although hyperchloraemic acidosis occurred more frequently with normal saline, the study was too small to show the beneficial or harmful effects of balanced crystalloids on clinically relevant outcomes.[16] During renal transplantation, Ringer's lactate or Plasma-Lyte 148 reduced the incidence of metabolic acidosis compared to saline, but does not lead to better postoperative renal function.[17,18]

In summary, the use of normal saline can increase the risk for hyperchloraemic metabolic acidosis in large volume administration. There is a need to elucidate in large comparative studies whether balanced solutions are associated with a favourable profile in view of postoperative morbidity when compared to normal saline.

Hypokalaemia and hyperkalaemia

In contrast to normal saline and colloids, balanced i.v. fluids contain potassium at a concentration similar to that of the extracellular fluid (4–5 mmol litre^{-1}). Potassium is a predominantly intracellular ion, and supplemental potassium has a large volume of distribution. It is currently unclear whether balanced i.v. fluids reduce the incidence of hypokalaemia and related complications, such as arrhythmias or cardiac arrest. However, direct potassium supplementation did not reduce postoperative atrial fibrillation in cardiac surgery.[19] In renal transplantation, the use of balanced crystalloids instead of normal saline reduces the risk for hyperkalaemia.[17,18] This is attributed to the transcellular potassium shift as a result of a hyperchloraemic acidosis with normal saline, which is more significant than the low concentrations of potassium present in balanced i.v. fluids.

HESs and renal function

The use of HES has become controversial in the past two decades after an increasing number of studies in critically ill patients, showing that its administration was associated with an increased incidence of AKI or even mortality.[20,21] Although the discussion on the use of HES in critically ill patients is beyond the scope of the current review, in some of these trials there were substantial concerns regarding methodology.[22] For example, in some studies, HES was administered before randomisation, the assessment of hypovolaemia was insufficient, there was prolonged administration of HES, or the administered volume surpassed the maximum dose.[22]

The use of HES 130/0.4 was studied in several small randomized controlled trials (RCTs) involving abdominal, orthopaedic, or vascular surgery.[23–29] In all studies, HES 130/0.4 did not increase the risk for AKI compared to crystalloids or gelatine. Two RCTs in liver transplantation showed no deleterious effect of HES 130/0.4 on renal function compared to albumin 5% or gelatine 4%.[30,31] Notably, in most of the aforementioned studies, the total dose of HES surpassed the maximum dose currently recommended by the European Medicines Agency.[26–31] Moreover, none of the RCTs were powered to detect a difference in AKI between modern-generation HES and crystalloids in the surgical patient. The quality and level of evidence of the available literature are too low to conclude whether HES has a favourable or unfavourable profile in the treatment of acute perioperative hypovolaemia. When HES is used, the recommended dose should not be surpassed, and its use should be restricted to non-septic patients without pre-existent renal failure.

Effect of fluids on haemostasis

Haemodilution is associated with the dilution of coagulation factors. Moreover, experiments *in vitro* suggest that haemodilution with colloids has a greater effect on haemostatic parameters, such as clotting time (CT) and clot firmness, than haemodilution with crystalloid solutions. Indeed, experiments *in vivo* showed that 30% haemodilution by unbalanced HES 130/0.4 resulted in a relatively high reduction in fibrinogen and thrombin concentrations (44%),[32] and HES also seems to have a greater impact on *in vitro* coagulation parameters than gelatine- and albumin-containing solutions.[33] Several studies have investigated the effect of distinct fluid types on coagulation parameters in surgical patients, including laboratory coagulation tests, such as activated partial thromboplastin time, prothrombin time, platelet count, and fibrinogen concentrations,[30,34–38] or the point-of-care thromboelastographic *R* and maximum amplitude,[39,40] or the thromboelastometric EXTEM CT and EXTEM and FIBTEM maximum clot firmness.[41–43] For detailed information, see Supplementary Table 1. Most studies did not show a difference in coagulation parameters between different fluid types, except for the older-generation HES 670/0.75, which was associated with the deterioration of coagulation parameters compared to Plasma-Lyte 148[41] or HES 130/0.4.[36,39] Most of these studies were limited by a small sample size and had different dosing strategies.

Table 2 shows RCTs comparing different fluid types with perioperative blood loss as the primary end point.[44–52] The majority of studies were performed in the cardiac surgical setting and did not show a difference in 24 h blood loss between HES, albumin, gelatine, or crystalloid solutions. The only study showing a difference in postoperative blood loss was performed in cystectomy, with a favourable haemostatic profile for Ringer's lactate compared to HES 130/0.4 (blood loss 1370 [603] *vs* 2181 [1190] ml; P=0.038).[48] However, the same authors could not repeat these findings in two comparative studies in a similar population when comparing Dextran 70 or albumin 5% with Ringer's lactate.[49,50] In conclusion, the majority of studies do not show a difference in blood loss between fluid types. These data should be viewed in light of different dosing strategies and populations amongst studies. Moreover, in most studies comparing colloids and crystalloids as resuscitation fluids, the total volume of fluids administered is different between groups, and paralleled by maintenance infusion of a crystalloid. It is, therefore, difficult to differentiate between the direct effects of a fluid type on haemostasis and the dilution component of fluid resuscitation.

The use of HES as the main component of the priming solution for extracorporeal circulation during cardiac surgery was compared to gelatine[53] or albumin.[54,55] In these studies, the secondary end points postoperative bleeding and allogeneic blood transfusion were not different between groups. In an RCT, there were no differences in blood-coagulation parameters or postoperative bleeding between the use of Ringer's acetate or balanced HES 130/0.4 as the priming solution.[56] The HES group required more postoperative blood transfusion, albeit the study was not powered to prove this effect.[56] Moreover, a large dose of HES 130/0.4 did not reveal differences in postoperative blood loss and bleeding after

Table 2 Overview of randomized controlled studies with perioperative blood loss as primary end point. aPTT, activated partial thromboplastin time; CABG, coronary artery bypass graft surgery; CT, clotting time; HES, hydroxyethyl starch; INR, international normalized ratio; MA, maximum amplitude; MCF, maximum clot firmness; PRBC, packed red blood cell; PT, prothrombin time; TEG, thromboelastography; TEM, thromboelastometry. *Maintenance fluid.

Author	Fluids compared	Procedure	*In vitro* parameters (during/end of surgery)	Clinical parameters	Conclusion
Primary end point: perioperative blood loss					
Hanart and colleagues[47]	1: Albumin 4% 2: HES 130/0.4	Paediatric cardiac surgery (n=100)	aPTT (s): 44 (41–49) *vs* 44 (40–52) PT (%): 60 (52–65) *vs* 55 (50–64) Fibrinogen (mg dl^{-1}): 160 (138–185) *vs* 144 (120–165) Platelets ($\times 10^9$ litre^{-1}): 171 (136–205) *vs* 151 (111–183)	Blood loss in 24 h (ml): 53 (36–74) *vs* 53 (34–73) Total transfusion rate: 78% *vs* 57%; P=0.0188)	No difference in 24 h blood loss between albumin 4% and HES 130/0.4
Kasper and colleagues[44]	1: HES 130/0.4 (<50 ml kg^{-1}) 2: HES 200/0.5 (<30 ml kg^{-1}) (+gelatine*)	CABG (n=120)	aPTT (s): 65 [29] *vs* 69 [27] PT (INR): 1.2 [1.0] *vs* 1.2 [1.0] Fibrinogen (g litre^{-1}): 2.3 [0.8] *vs* 2.2 [0.8] Platelets ($\times 10^9$ litre^{-1}): 139 [43] *vs* 127 [39]	Blood loss in 24 h: 660 (380–1440) *vs* 705 (330–1750) ml; P=0.60 PRBC transfusion in 24 h: 0 (0–3) *vs* 0 (0–4) units; P=0.17	No difference in 24 h blood loss between HES 130/0.4 and HES 200/0.5
Kimenai and colleagues[45]	1: HES 130/0.4 (<50 ml kg^{-1}) 2: Gelatine (+saline or Ringer's lactate*)	CABG (n=60)	EXTEM MCF (mm): 61 [5] *vs* 61 [6] (P=0.47) FIBTEM MCF (mm): 12 [5] *vs* 11 [3] (P=0.93)	Blood loss in 24 h: 500 [420] *vs* 465 [390] ml; P=0.48	No difference in 24 h blood loss between HES 130/0.4 and gelatine
Lee and colleagues[52]	1: Balanced crystalloid 2: HES 130/0.4 (<30 ml kg^{-1}) (+balanced crystalloid)	CABG (n=106)	TEG R (min): 22.6 [15.6] *vs* 28.4 [19.8]; P=0.163 TEG MA (mm): 43.6 [10.4] *vs* 40.0 [10.8]; P=0.147	Blood loss in 24 h: 810 [322] *vs* 753 [313]; P=0.353 PRBC transfusion in 24 h: 0.9 [1.0] *vs* 0.6 [1.1]; 0.508	No difference in 24 h blood loss between a balanced crystalloid and HES 130/0.4
Rasmussen and colleagues[48]	1: HES 130/0.4 (35 ml kg^{-1}) 2: Ringer's lactate (35 ml kg^{-1})	Cystectomy (n=33)	TEG MA (mm): 52.1 [7.5] *vs* 63.6 [5.3]; P=0.001 Fibrinogen (μmol litre^{-1}): 5.09 [1.79] *vs* 7.68 [2.11]; P=0.001 Platelets ($\times 10^9$ litre^{-1}): 154 [31] *vs* 217 [49]; P=0.02	Blood loss (ml): 2181 [1190] *vs* 1370 [603]; P=0.038 PRBC transfusion (ml): 286 [380] *vs* 62 [169]; P=0.041	More blood loss in the HES 130/0.4 group compared to the Ringer's lactate group
Rasmussen and colleagues[49]	1: Dextran 70 (25 ml kg^{-1}) 2: Ringer's lactate	Cystectomy (n=37)	TEG MA (mm): 48.9 (44.6–53.2) *vs* 62.1 (58.9–65.3); P=0.001	Blood loss (ml): 2339 [1470] *vs* 1822 [1240]; P=0.27 PRBC transfusion (ml): 597 [613] *vs* 313 [545]; P=0.14	No difference in blood loss between dextran 70 and Ringer's lactate
Rasmussen and colleagues[50]	1: Albumin 5% (25 ml kg^{-1}) 2: Ringer's lactate	Cystectomy (n=39)	TEG MA (mm): 60 [7] *vs* 68 [6]; P<0.002	Blood loss (ml): 1658 (800–3300) *vs* 1472 (700–4330); P=0.45 PRBC transfusion (ml): 235 (0–980) *vs* 80 (0–1100); P=0.14	No difference in blood loss between albumin 5% and Ringer's lactate
Skhirtladze and colleagues[46]	1: Albumin 5% (<50 ml kg^{-1}) 2: HES 130/0.4 (<50 ml kg^{-1}) 3: Ringer's lactate (<50 ml kg^{-1}) (+Ringer's lactate*)	Cardiac surgery (N=240)	FIBTEM MCF (mm): 10 (9–13) *vs* 7 (6–10) *vs* 13 (11–17); P<0.0001	Blood loss in 24 h (ml): 835 (545–1253) *vs* 700 (540–1090) *vs* 670 (455–1015); P=0.085 PRBC transfusion rate: 58% *vs* 61% *vs* 34%; P=0.0013	No difference in 24 h blood loss between albumin 5%, HES 130/0.4, and Ringer's lactate
Van der Linden and colleagues[51]	1: HES 130/0.4 (<50 ml kg^{-1}) 2: Gelatine (<50 ml kg^{-1}) (+Plasma-Lyte 148*)	CABG (n=132)	Unavailable	Total blood loss (ml kg^{-1}): 19.4 [12.3] *vs* 19.2 [14.5] Total PRBC transfusion: 0 (0–6) *vs* 0 (0–6) units	No difference in blood loss between HES 130/0.4 and gelatine

cardiopulmonary bypass compared to a 200/0.5 starch.[44] The level of evidence that is available to support the choice of fluid type in priming solution is low. However, based on the unfavourable profile of HES in critically ill patients or patients with renal failure, HES is decreasingly used for cardiopulmonary bypass prime solutions.

Physiology

Viscosity and microvascular perfusion

The reduction in haematocrit after high-volume fluid resuscitation with crystalloids or colloids leads to a decrease in whole blood viscosity. In addition to their effect on colloid osmotic pressure, colloids were designed to mimic plasma viscosity after dilution with blood during fluid resuscitation, with a target viscosity of 1.0–1.2 cP.[57] Although gelatine has a lower intrinsic viscosity than HES, its effect on red blood cell aggregation leads to increased viscosity *in vivo* compared to HES.[58]

In the microcirculation, relative viscosity is lower than in larger vessels, the so-called Fåhræus–Lindqvist effect, and a reduction in haematocrit can, therefore, be of particular influence on capillary blood flow and capillary density (Fig 1).[59,60] Most studies focusing on the effects of different fluid types on viscosity and microcirculatory function are limited to experimental animal studies. In a hamster model, an increase in blood viscosity by highly viscous colloids attenuated the impairment of capillary perfusion induced by extreme haemodilution.[61] The benefit of high-viscosity colloids on capillary perfusion during haemodilution is attributed to the preservation of intra-capillary pressure that is needed to maintain perfusion.[60] A comparison of polyethylene-glycol-conjugated bovine serum albumin[62] or human haemoglobin[63] with HES during resuscitation after haemorrhage in hamsters revealed that, in contrast to HES, the conjugated albumin provided a prolonged restoration of microcirculatory function, suggesting a different impact of colloid solutions on the microcirculation.[62,63] A recent systematic review summarising the experimental evidence for optimal fluid choices in post-haemorrhagic shock resuscitation suggests that fluids with a high viscosity, high colloid osmotic pressure, and restorative capacities for the endothelial glycocalyx have the most favourable profile to restore microcirculatory function.[64] From a clinical perspective, the evidence for the most effective fluid-resuscitation strategy to improve microcirculatory perfusion is, however, limited, and until now, the available evidence only suggests that artificial colloids are inferior in the restoration of microcirculatory oxygenation when compared to packed red blood cell transfusion.[65]

Endothelial glycocalyx

The glycocalyx resides on the surface of the vascular endothelium and consists of a layer of proteoglycans (e.g. syndecan and receptor-bound hyaluronan). The glycocalyx is negatively charged and contributes to the natural barrier of the vessel wall.[66] It has a fragile structure and can be released by multiple stimuli, for instance, ischaemia and reperfusion, sepsis, hypoxia, inflammatory activation, hyperglycaemia, and hypervolaemia.[67] As the total volume of the endothelial glycocalyx is estimated at 700 ml, glycocalyx shedding can significantly influence fluid shifts, even independently from its function in the endothelial barrier. Moreover, the glycocalyx plays a role in the mechanical transduction of shear stress to the endothelium, and inhibition of leucocyte or platelet adhesion to the vascular wall.[66]

In a systematic review of preclinical studies, it was concluded that fresh frozen plasma (FFP), but not Ringer's lactate, normal saline, or HES, partially restores glycocalyx thickness, with concomitant benefits for microcirculatory perfusion, after haemorrhagic shock.[64] In a more recent publication, it was suggested that the larger plasma volume expansion by FFP or albumin compared to crystalloids after haemorrhagic shock could account for most of the favourable effects on outcome, as plasma concentrations of endothelial glycocalyx components were similar between groups.[68] However, the better volume effects of FFP or albumin compared to Ringer's acetate suggest that FFP and albumin increase glycocalyx restoration rather than prevent its degradation. Others showed that albumin appears to be more effective than HES for glycocalyx restoration.[69,70] Studies in guinea pig heart preparations found that artificial colloids were less damaging to the endothelial glycocalyx than normal saline.[69,71]

The number of comparative clinical studies evaluating different fluid types and their effect on glycocalyx integrity is limited, and these studies mostly focus on glycocalyx-shedding products. In an observational study, a prophylactic bolus of 750 ml warmed lactated Ringer's solution before spinal anaesthesia for Caesarean delivery was associated with a minor protein-adjusted median increase in heparin sulphate [from 600 (372–753) to 651 (424–895) ng mg^{-1}] and syndecan-1 [from 11 (8.4–16.1) to 12 (9.6–19.2) ng mg^{-1}].[72] In the only available RCT, it was hypothesized that older-generation HES (670/0.75) would lead to less endothelial damage and glycocalyx shedding than an equal dose of a balanced salt solution in off-pump cardiac surgery.[41] Median serum syndecan-1 concentrations were higher in the HES than in the crystalloid group after fluid infusion [79.9 (46.6–176.6) *vs* 62.7 (30.1–103.0) ng ml^{-1}; P=0.030), but this difference disappeared in the postoperative period.[41]

From these data, it can be concluded that the current literature lacks evidence with respect to the clinical impact of fluids on glycocalyx integrity. It is unclear whether a change in

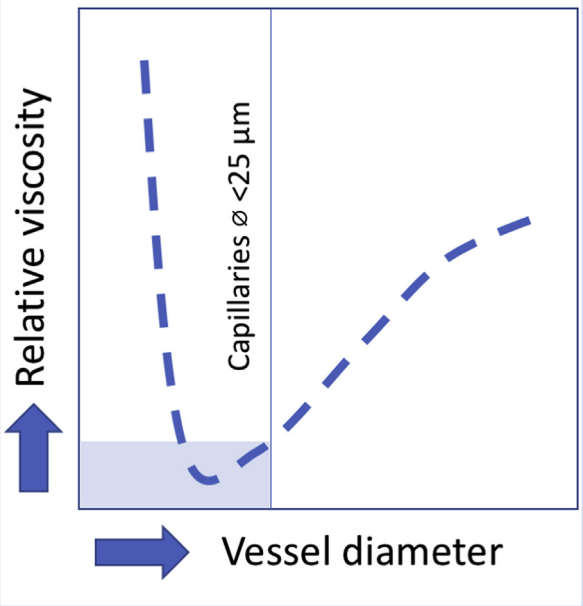

Fig 1. Schematic representation of the Fåhræus–Lindqvist effect in the microcirculation.

glycocalyx integrity has a clinically relevant impact on the final intravascular volume effect of distinct fluids. Moreover, it is unknown how this volume effect differs between healthy individuals and patients with dysfunction of the endothelial barrier. Further studies should reveal whether glycocalyx integrity is involved in the regulation of intravascular volume during fluid resuscitation, and not just a surrogate marker for a disease state.

Effect on colloid osmotic pressure

Colloid osmotic pressure is the osmotic pressure exerted by plasma proteins, and serves to attract fluid to the intravascular compartment. Although the absolute colloid osmotic pressure in plasma (~25 mm Hg) is low relative to the total osmotic pressure (~5500 mm Hg), it has a major contribution in fluid distribution because of the large difference between the intravascular and extravascular compartments. Starling's[73] equation describes the forces involved in fluid shifts between the intravascular and extravascular spaces as:

$$F = (P_c - P_i) - \sigma\,(\Pi p - \Pi i)$$

where F is the capillary filtration force, P_c is the capillary blood pressure, P_i is the interstitial pressure, σ is the osmotic reflection component, Πp is the plasma colloid osmotic pressure, and Πi is the interstitial colloid osmotic pressure (Fig 2).

More recently, it has become clear that the endothelial glycocalyx plays an important role in maintaining fluid in the intravascular compartment. The observations that there is no end-capillary fluid absorption from the interstitium at steady state and that filtration is relatively independent of the interstitial colloid osmotic pressure have led to a revised Starling equation (Fig 2), which has been reviewed extensively:[74,75]

$$F = (P_c - P_i) - \sigma\,(\Pi p - \Pi g)$$

where Πg is sub-glycocalyx colloid osmotic pressure.

In the revised Starling equation, there is an important role for the intact endothelial glycocalyx and the sub-glycocalyx space in the endothelial intercellular clefts. Experimental studies have shown that this space has a very low protein concentration, and thus, a low osmotic pressure, reducing the filtration of fluid from the capillaries.[74,75] Moreover, the presence of this low-protein space explains the absence of absorption at the venous end of the capillary, where the colloid osmotic pressure is higher in the interstitium than in the sub-glycocalyx space. As the endothelial glycocalyx has an osmotic reflection coefficient close to 1, indicating a low level of protein leakage through the endothelial barrier, the force opposing capillary blood pressure [$\sigma(\Pi p - \Pi g)$] roughly equals plasma colloid osmotic pressure.[74,75] The importance of plasma colloid osmotic pressure in the revised Starling equation is in line with early observations that low plasma colloid osmotic pressure is associated with tissue oedema.[76]

All i.v. fluids influence colloid osmotic pressure and fluid extravasation. Crystalloids lower plasma colloid osmotic pressure, whereas albumin, gelatine, and HES solutions increase plasma colloid osmotic pressure and intravascular volume. Hypertonic saline is an exception in the crystalloid group. It increases extracellular osmotic pressure, but lowers colloid osmotic pressure, therefore, attracting water from the intracellular compartment into the extracellular space, but not specifically into the intravascular compartment. Hypertonic saline has been used extensively to reduce intracranial pressure in traumatic brain injury, but no survival benefits were observed in comparison with other fluids.[77]

In an animal model, albumin was more effective than HES in reducing extravasation of fluids for a similar colloid osmotic pressure, which is attributed to the incorporation of albumin in the endothelial glycocalyx.[69] In acute inflammation, tissue oedema develops as a consequence of a reduced osmotic reflection coefficient through increased endothelial permeability and glycocalyx shedding. Consequently, the efficacy of colloids for intravascular volume expansion is reduced during inflammatory conditions.[69]

Intravascular volume effects

Crystalloids can freely pass the glycocalyx, whilst colloids are largely retained within the vasculature in case of an intact glycocalyx.[78,79] Many studies have investigated the intravascular volume effect of fluid therapy in hypervolaemic conditions, such as volume loading, but have low clinical relevance. For instance, atrial natriuretic peptide is released during hypervolaemia, which leads to endothelial glycocalyx shedding, and thus, reduces the intravascular volume effect of i.v. fluids, particularly for colloids.[80]

In acute normovolaemic haemodilution experiments in human subjects as a model for acute blood loss, 17% of infused Ringer's lactate remained intravascular.[81] Plasma volume was subsequently restored and interstitial oedema that developed after Ringer's lactate infusion was reduced by infusing albumin 20%. It remains unknown whether this could be attributed to the increased competence of the endothelial glycocalyx, increased plasma colloid osmotic pressure, or both.[81] In contrast to changes in plasma volume after infusion of Ringer's lactate, acute normovolaemic haemodilution with albumin 5% resulted in a comparable blood volume to preoperative values.[79] In healthy volunteers, replacement of 900 ml of blood by albumin 5% or Ringer's lactate resulted in better maintenance of cardiac output and blood volume in the albumin group compared to the Ringer's lactate group.[82] Similarly, almost the entire volume of HES 130/0.4 6% remained in the intravascular space during acute normovolaemic haemodilution.[83]

From these results, it follows that restoration of intravascular volume after acute hypovolaemia is most effective using colloids, whereas maintenance or restoration of the entire extracellular volume is best performed with crystalloids. This is the approach to fluid therapy that is most often used in perioperative goal-directed therapy protocols.[84,85] Moreover, the Colloids versus Cristalloids for the Resuscitation of the Critically Ill (CRISTAL) trial showed that colloids were not more harmful than crystalloids when used for the restoration of hypovolaemia.[86] These findings are difficult to translate to the perioperative setting, however, as only critically ill patients with hypovolaemic shock were included. Because of pragmatic reasons, the study was not blinded, and physicians were allowed to use any crystalloid or colloid available in their institution, leaving the study open to bias.[86] More randomized clinical trials that evaluate this strategy in the perioperative setting are awaited, particularly whether the efficacy of colloids in the restoration of intravascular volume during acute hypovolaemia outweighs their potential side-effects in surgical patients.

Specific clinical indications

We performed a semi-structured literature search in PubMed with the MeSH search terms [Surgical Procedures], [Fluid

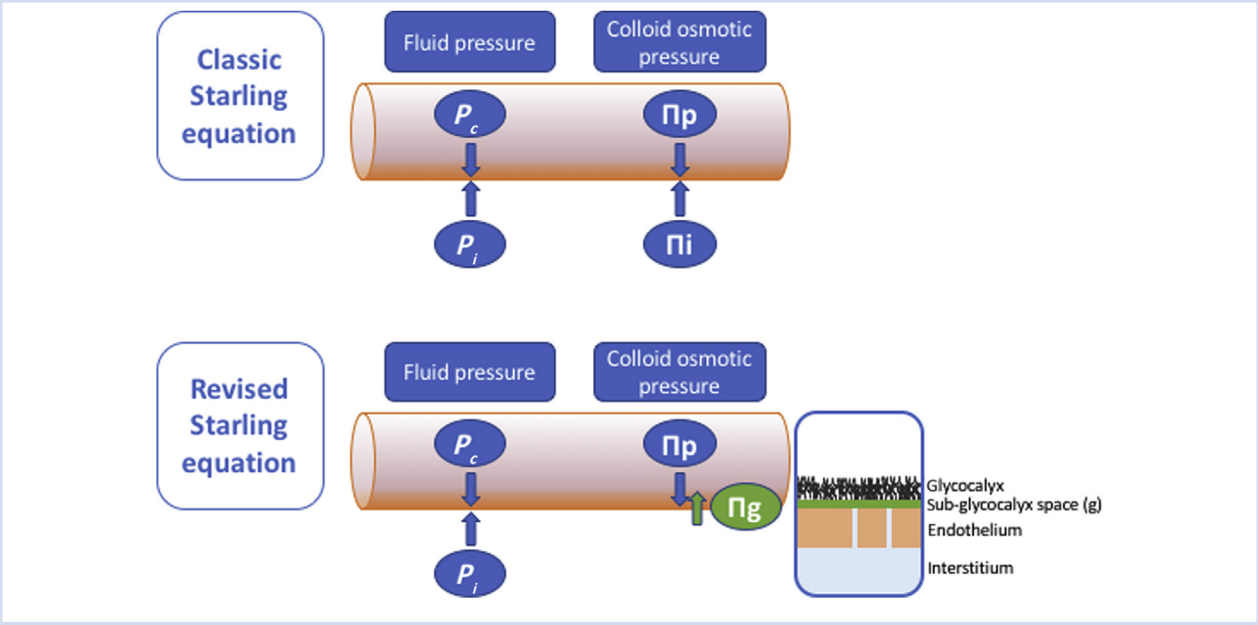

Fig 2. Schematic representation of the classical and revised Starling equations. P_c = capillary blood pressure; P_i = interstitial pressure; Πp = plasma colloid osmotic pressure; Πi = interstitial colloid osmotic pressure; Πg = sub-glycocalyx colloid osmotic pressure.

Therapy], and [Colloids] (112 727 hits). All fluid types summarized in Table 1 were included (unbalanced and balanced crystalloids, and HES-, gelatine-, and albumin-containing colloids). This search was narrowed for the years 1997–2017 (69 411 hits) and clinical trials and humans, and excluding [SEPSIS] (5020 hits). The search was combined with specific clinical indications or end points, including cardiac surgery, renal transplantation, neurosurgery, traumatic brain injury, major abdominal surgery, paediatric surgery, and major haemorrhage to provide an overview of the clinical trials in this area. The search was mainly limited to RCTs (Supplementary Tables 2 and 3, respectively) that were graded for quality based on the Oxford Centre for Evidence-based Medicine—Levels of Evidence definitions. Clinically relevant end points included major adverse cardiac events (MACEs), AKI, blood loss, length of stay (LOS) in the ICU, length of hospital stay (LOHS), and mortality. Studies that only reported blood loss as relevant clinical end point are described in Table 2.

Cardiac surgery

Eleven RCTs in cardiac surgery were identified with other primary clinically relevant end points than postoperative bleeding (Supplementary Table 2). In studies where HES was compared to a crystalloid solution, no differences were found in the LOS in the ICU or total LOHS between groups.[41,46,52,87–89] Amongst studies including HES and crystalloid fluid resuscitation, there was only one study reporting an increased 24 h blood loss in the HES group compared to the crystalloid group.[41] There were no indications of higher rate of MACE or AKI in patients exposed to HES compared to crystalloid.[41,46,52] In two studies, distinct HES fluids were compared, reporting similar mortality rates between a balanced and unbalanced HES,[90] and comparable LOHS between HES 130/0.4 and HES 200/0.5.[44] In a small study, a comparison of albumin 4% with Ringer's lactate in the priming solution revealed no difference in length of ICU stay.[91] Two studies comparing a gelatine fluid with either Ringer's lactate[92] or HES 130/0.4[51] did not demonstrate differences in atrial fibrillation rates or LOS.

From the aforementioned studies, we cannot conclude that there is a difference in the number of cardiovascular complications, AKI rates, or LOHS amongst fluid-resuscitation strategies. However, most studies included in this review have small sample sizes based on power calculations using clinically irrelevant end points, and are rated as low-quality studies with respect to their level of evidence.

Renal transplantation

Renal transplantation requires optimal hydration and perfusion of the kidney to ensure normal function and prevent acute tubular necrosis. Crystalloid fluid therapy is the first choice in renal-transplantation procedures, but infusion of large volumes of normal saline is associated with the development of hyperchloraemia. Three RCTs investigated the differences in acid–base balance and rates of hyperchloraemia and hyperkalaemia between normal saline or Ringer's lactate during renal transplantation.[17,93,94] Normal saline increases serum chloride and potassium concentrations, and alters base excess compared to Ringer's lactate, whilst Ringer's lactate was associated with increased lactate concentrations, but without differences in creatinine clearance levels.[17,93] The number of patients requiring dialysis after renal transplantation did not differ between normal saline and Ringer's lactate group rates.[17,93] Three studies compared normal saline with Plasma-Lyte 148 or an alternative balanced crystalloid in renal-transplantation surgery.[18,93,95,96] Plasma-Lyte 148 fluid resuscitation resulted in the maintenance of the acid–base balance and potassium concentrations, but without differences in postoperative renal function or graft rejection amongst groups.[18,93,95] In addition, the use of albumin 20% as an alternative of normal saline did not show any benefit regarding graft function after surgery.[97]

All aforementioned studies were small in size, and larger RCTs are required to show whether there is a benefit of a balanced crystalloid solution with respect to clinically relevant outcome measures, such as renal function and graft rejection.

Neurosurgery

Maintenance of the plasma osmotic pressure during neurosurgical procedures could contribute to reduced complications, including cerebral oedema and intracranial hypertension. Consequently, neurosurgical procedures, which generally have a relatively long duration, are preferably performed using isotonic crystalloid solutions that reduce the risk for hyperchloraemia and metabolic acidosis.[12]

The administration of a balanced crystalloid with colloid was associated with lower serum chloride concentrations and maintenance of acid–base balance compared to unbalanced crystalloid in combination with an unbalanced colloid.[98] A comparative study of isotonic and hypertonic HES 130/0.4 solutions in brain-tumour surgery revealed reduced fluid load with lower dural tension scores and better brain relaxation in the hypertonic group.[99] Two RCTs in patients undergoing neurosurgery in the prone position showed that the use of HES 130/0.4 resulted in lower fluid requirements compared to Ringer's acetate.[43,100]

In patients with traumatic brain injury, special attention should be paid to the effect of i.v. fluids on intracranial pressure. Hypertonic saline and mannitol are frequently used to reduce intracranial pressure by increasing plasma osmotic and colloid osmotic pressures, respectively. A recent meta-analysis showed no difference in the effectiveness in lowering intracranial pressure between hypertonic saline and mannitol, whilst hypertonic saline had fewer side-effects than mannitol.[101,102] A subgroup of brain-injury patients was included in a *post hoc* analysis of the Saline versus Albumin Fluid Evaluation (SAFE) trial, in which albumin 4% was compared with normal saline in the intensive-care setting, with less favourable outcome in patients resuscitated with albumin.[103] This might be attributed to the effect of albumin crossing the damaged blood–brain barrier, or to the hypo-osmolarity of albumin 4% (260–266 mOsm kg^{-1}), leading to increased intracranial pressure.[104] As most balanced crystalloids are hypo-osmolar, they are not suitable for use in traumatic brain injury.[105] The effect of albumin or artificial colloids in isotonic fluids on outcome in traumatic brain injury has not been investigated.

The number of studies focusing on intraoperative fluid therapy in neurosurgical procedures is small, and none of the studies was designed to show differences in clinically relevant end points. However, the aforementioned studies suggest that the use of hypertonic fluids or artificial colloids contributes to reduced fluid load and maintenance of cerebral physiology during surgery.

Major abdominal surgery

Twelve studies in major abdominal surgery were identified, in which the effects of i.v. fluids were compared on clinically relevant outcomes (Supplementary Table 3). Artificial colloids (HES and dextrans) were compared to crystalloids (both balanced and unbalanced) in seven of the selected studies.[26,27,30,48,49,106,107] In two studies, blood loss was increased in the HES group compared to the crystalloid group, albeit that blood loss was only a primary end point in the cystectomy study.[26,48] The use of dextrans was associated with more major blood loss (>1500 ml) compared to Ringer's lactate.[49]

None of the studies detected a difference in cardiovascular or renal complications between artificial colloids and crystalloid fluid resuscitation in major abdominal surgery. The length of ICU stay was 2 h longer in patients undergoing gastrointestinal surgery with HES 70/0.5 *vs* Ringer's acetate, which might be considered a clinically irrelevant difference.[106] In a study where HES 130/0.4 was compared to normal saline in cytoreductive ovarian cancer surgery, a trend towards an increased 3 month mortality in the HES group was observed (n=5 *vs* n=0, respectively; P=0.051).[107] However, all deaths were assessed as being unrelated to the study intervention before unblinding of the study subjects.

Albumin 5% was compared to Ringer's lactate in radical cystectomy and to HES 130/0.4 during liver transplantations.[30,50] Albumin did not lead to altered outcome in terms of blood loss, AKI, or LOHS compared to Ringer's lactate in either study.[30,50] In the study focusing on renal function during liver transplantation, one out of 20 patients in both HES and albumin groups required renal replacement therapy. Assessment of renal failure and ICU and hospital stay and mortality was similar between groups.[30]

One study assessed the effects of Ringer's lactate and normal saline in abdominal aortic surgery.[108] Normal saline led to increased incidence of hyperchloraemic acidosis and a trend towards more blood loss, although this did not lead to an increased incidence of cardiovascular or renal morbidity.[108] Also, a comparison of hypertonic saline with Ringer's lactate in pancreaticoduodenectomy did not reveal any differences in postoperative complications.[109] In contrast, a comparison of Plasma-Lyte 148 and Ringer's lactate in liver-resection surgery, with HES 130/0.4 as additional fluid, showed more blood loss in the Ringer's lactate group [500 (300–638) *vs* 300 (200–413) ml; P=0.03], but without reporting other clinically relevant differences in outcome.[35]

In conclusion, only blood loss might be increased by HES or dextran administration during major abdominal surgery, but no other clinically relevant outcome parameters were affected by i.v. fluid choice in major abdominal surgery. However, our conclusion should be handled cautious, as almost all existing studies were small and not powered to detect a difference in clinical outcome.

Paediatric surgery

Fluid resuscitation with albumin solutions is still a preferred practice in major paediatric surgery. In particular, unbalanced synthetic colloids contribute to metabolic acidosis, as shown in children of 0–12 yr undergoing major surgery.[110] In order to evaluate whether the use of synthetic colloids is associated with adverse outcomes compared to albumin solutions, four studies compared the use of HES 130/0.4 with albumin for intraoperative volume-replacement therapy in children aged 5–46 months,[47] 3–15 months,[111] 0–2 yr,[112] and 2–12 yr.[113] All studies showed an equivalent efficacy for both colloid solutions, without reporting differences in adverse effects.[47,111–113] Two studies reported that albumin was associated with higher blood-transfusion requirements.[47,111] A propensity-matched analysis later confirmed that HES during paediatric cardiac surgery is as safe as albumin, probably with less fluid accumulation.[114] The effect of HES 70/0.5 *vs* Ringer's lactate on haemoglobin concentrations was further measured in infants and toddlers (1–38 months) undergoing urological surgery,

showing that HES was a more effective volume expander than Ringer's lactate, without reporting a difference in adverse effects amongst groups.[115]

Unfortunately, the number of studies focusing on the choice of fluid type in children is small. Current data suggest no superiority of one fluid over the other, but unbalanced fluids that alter the acid–base balance in children should be avoided, whilst HES is considered as a safe alternative for albumin.

Acute major bleeding

Large volume resuscitation can contribute to prolonged bleeding in major traumatic bleeding or obstetric haemorrhage. In particular, the acidosis associated with unbalanced crystalloids might further contribute to the lethal triad of coagulopathy during major bleeding.[116] In the prehospital treatment of traumatic hypovolaemic shock, two small studies showed that hypertonic fluid resuscitation does not improve outcome compared to other crystalloids, and can even worsen the coagulation status.[117,118] In a propensity-matched analysis of women receiving HES 130/0.4 or balanced crystalloids, no association was observed between HES use and perioperative blood loss during caesarean delivery.[119]

The fourth edition of The European guideline on management of major bleeding and coagulopathy following trauma recommends that isotonic crystalloid solutions are the first choice in fluid resuscitation in hypotensive trauma, and colloids should be avoided because of their adverse effects of haemostasis.[120] However, the latter is mainly based on studies in intensive care or septic patients, and novel RCTs are required to support the right choice of resuscitation fluids in acute traumatic bleeding.

Conclusions

Patient-tailored fluid management can contribute to improved outcomes in the perioperative setting. The majority of studies in this field focus on goal-directed approaches, thereby tailoring the need for volume to individual requirements.[4,5,85]

The choice of fluid type is of particular interest with the increasing number of reports showing higher rates of hyperchloraemia, hyperkalaemia, and metabolic acidosis associated with the use of large volumes of normal saline, and the association of HES with bleeding disorders and renal complications in the critically ill. The unfavourable observations that were attributed to HES in the critically ill were also of impact on the perioperative setting. In particular, in some institutions, HES was replaced by gelatine or Ringer's lactate, which narrowed the available therapeutic strategies to treat perioperative hypovolaemia.

In the present review, we limited the available evidence for choice of fluid type to the perioperative setting, and focused on relevant clinical end points, including bleeding and transfusion, AKI, and LOHS. From this analysis, we conclude that large volumes of normal saline are associated with disturbance in the acid–base balance, which can be detrimental in particular populations, including neurosurgery, acute major bleeding, and children. Only a few studies included in this review report the deleterious effects of HES on the bleeding status of the patient, without revealing unfavourable effects on cardiac or renal function.

These findings should be considered in view of the low quality and small sample size of most available studies. The publication of two ongoing RCTs focusing on clinically relevant end points in the perioperative setting[121–123] may shed (some) light on our knowledge and improve the available level of evidence regarding the efficacy and safety of different fluid types in the surgical patient.

Authors' contributions

Literature search: all authors.
Drafting and revising paper: all authors.
Final approval of paper: all authors.

Declaration of interest

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bja.2017.10.022.

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