The Place for Starches and Other Colloids

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IFA Commentary (MLNGM)

This chapter provides a review of the different types of colloids mainly hydroxy-ethyl starch (HES) solutions and the differences between balanced and unbalanced starches. It tackles many questions like the never-ending crystalloid vs. colloid debate: Where are we now? Is there merely a difference in cosmetics or also in outcome? What are the strengths and flaws of the different big fluid trials and meta-analyses? Are there specific situations or patient groups where colloids behave differently and may have an advantage? This chapter will basically focus on the results of five major trials comparing the use of crystalloids versus colloids in critically ill patients: The 6S and VISEP study, the CRYSTMAS trial, the CRISTAL study, and the CHEST trial.

At the time of the First International Fluid Academy Day in November 2011, the evidence base for the use of colloids versus crystalloids in critically ill patients was rather weak. Except for the SAFE and VISEP studies, no randomized intervention studies were available. Crucially, neither of these addressed the use of the more recent lower molecular weight starch derivatives (HES 130) or the use of 'balanced' solutions. Subgroup analysis and meta-analysis indicated equipoise for most subgroups, with the exception of trauma patients where harm could be expected with the use of colloids on one side and sepsis, cardiopulmonary bypass, and malaria patients on the other side where the use of albumin might be advantageous. In the '6S study' and the 'CHEST trial', the colloid was one of the HES 130 solutions, and, while failing to find benefit of these solutions in critically ill patients, both trials indeed confirmed earlier suspicions of renal damage associated with them. The EMA's safety committee, PRAC, suspended in 2013 the use of HES solutions in critically ill, septic, and burn patients or those with kidney injury. HES solutions could only be used in the perioperative setting, e.g., haemorrhagic shock.

However, many questions and controversies remained: Is molecular weight the only parameter that counts or do we need to take into account the charge? Are smaller starches safer and is the origin of the starch (maize vs. potatoes) important? Does the buffer solution in balanced solutions (lactate, acetate, malate, etc.) matter? Do we have to fear for the kidneys and the coagulation with the latest perioperative indications for starches? Should we bother about anaphylactic reactions or prior disease when using gelatins? What to use in haemorrhagic shock: colloids or crystalloids or just blood products? However, the final curtain may fall over HES as EMA's safety committee, PRAC, has recommended in February 2022 that the marketing authorizations for HES solutions for infusion should be suspended across the European Union. This was based on new results of an ongoing safety analysis which showed that HES solutions for infusion are still being used outside the recommendations included in the product information. The committee concluded that the further restrictions introduced in 2018 have not sufficiently ensured that the medicines are used safely and that HES solutions continue to be used in certain groups of patients in whom serious harm has been demonstrated.

Learning Objectives

After reading this chapter, you will understand that:

1. Various types of colloids can be used in critically ill and perioperative patients.
2. Structures, properties, benefits, and harms of synthetic colloids are listed.
3. Evidence for use of synthetic colloids is reviewed.
4. Starches should no longer be used in critically ill patients with sepsis, burns, and kidney injury.

Case Vignette

A 74-year-old male with a past history of poorly controlled diabetes mellitus with diabetic nephropathy and coronary artery disease with severe left ventricular systolic dysfunction (global ejection fraction ~25%) was admitted to the coronary care unit with acute left ventricular failure. He was managed with medical therapy and required invasive ventilation support for the initial 2 days. On the fourth day of hospital stay, he developed fever and shortness of breath. On examination, he was a little confused with a heart rate 112/min, blood pressure 84/56 mmHg, respiratory rate 24/min, and SpO2 of 96% on 4 litres of O2. Chest X-ray showed new infiltrate in the left lower zone. Arterial blood gas revealed pH 7.36, PO2 64 mmHg, PaCO2 32.8 mmHg, HCO3 19.2 mmol/L, and lactate 4.6 mmol/L.

One of your colleagues suggested giving a bolus of 6% hydroxyethyl starch (140/0.4) for rapid correction of hypotension. He argued that the bolus of synthetic colloid will reduce the overall fluid requirement for this patient with septic shock and underlying cardiac dysfunction.

Questions

Q. What is the evidence in favour of or against the use of synthetic colloids in critically ill patients?

Introduction

Colloids, like crystalloids, are types of intravenous fluids used for resuscitation in critically ill, perioperative, or trauma patients. Colloids consist of large molecules which at least theoretically stay in the intravascular space for a longer duration before leaking into the interstitium. Colloids can be natural (e.g. human albumin, fresh frozen plasma) or synthetic (e.g. starches, gelatins, or dextran). Synthetic colloids were popular resuscitation fluids until a few years ago. However, they have lost their popularity because of increasing uncertainty about their benefit, high cost, and numerous adverse effects. In this chapter, we shall discuss various aspects of synthetic colloids including their role in current practice (Fig. 11.1). More information on crystalloid solutions can be found in Chap. 9, while albumin use is discussed in Chap. 10.
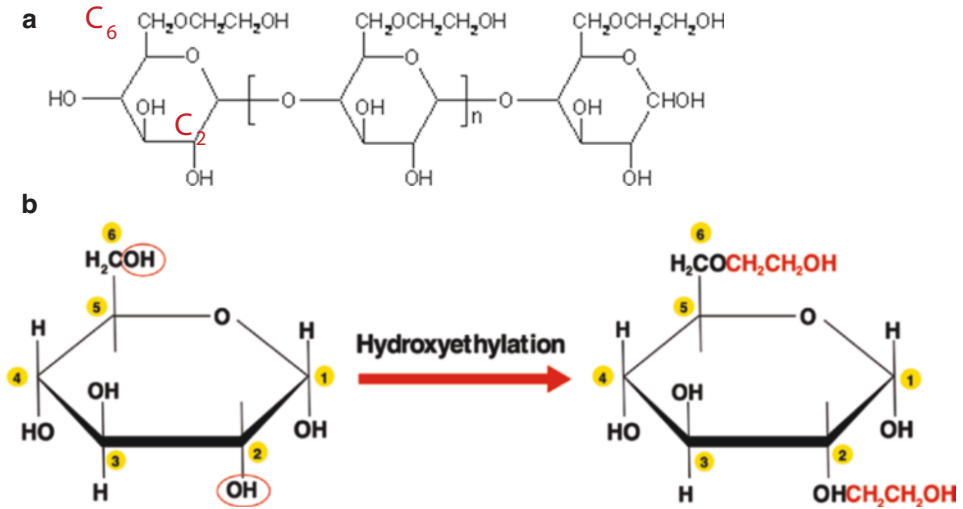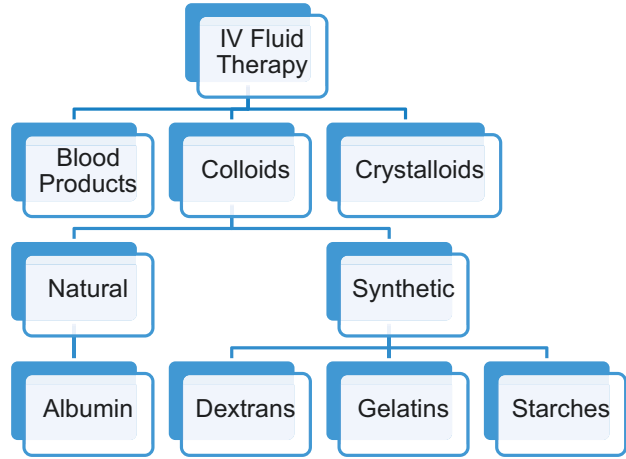
Fig. 11.1 Overview of
colloids

a

b

Fig. 11.2 (**a**) Schematic drawing of starch molecule. (**b**) Hydroxyethylation of starch molecule

Hydroxyethyl Starch Pharmacology

HES solutions are hydroxyethylated polysaccharides (carbohydrates) prepared from maize or potato (Fig. 11.2). The process of hydroxyethylation makes them relatively stable against degradation by alpha-amylase in serum and also increases their solubility. Typical commercially available HES product is characterized by three numbers: concentration of HES in solution (e.g. 6%), mean molecular weight (MW) (e.g. 200 kDa), and molecular substitution (MS) (e.g. 0.4) (Fig. 11.3). For example, a product labelled 6% HES 200/0.4

Fig. 11.3 Typical commercially available HES product is characterized by three numbers: concentration of HES in solution (e.g. 6%), mean molecular weight (MW) (e.g. 130 kDa), and molecular substitution (MS) (e.g. 0.42)
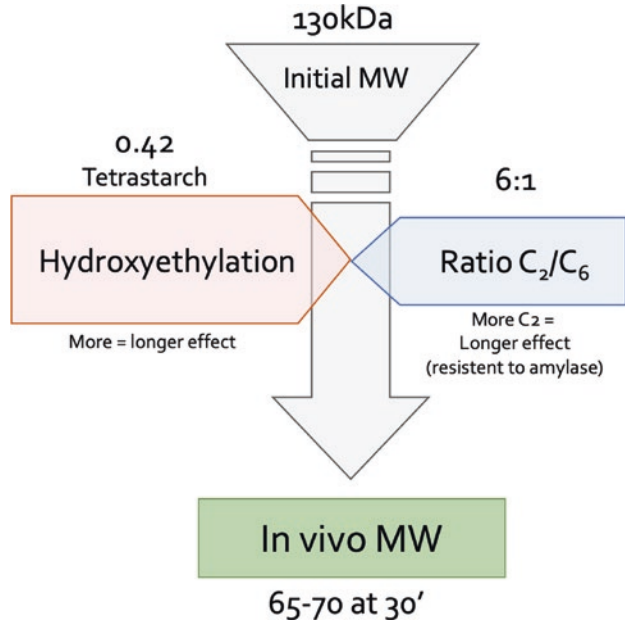
contains a 6% solution of HES of mean MW 200 kDa and a molecular substitution of 0.4. These properties influence the therapeutic profile as well as the adverse effects of a particular HES solution.

HES solutions are a polydisperse system consisting of particles of different molecular mass. The MW of a particular product denotes the average of these diversely sized particles. Osmotic effectiveness depends on the number of particles and not size and hence MW has little impact on the volume expanding effect of the solution. The concentration of HES in a solution determines the oncotic property of a particular HES solution. Commonly available concentrations are 6% and 10% which make them iso-oncotic and hyperoncotic, respectively. MS describes the degree of hydroxyethyl substitution per glucose unit. The higher the substitution, the more resistant it is to degradation by alpha-amylase and hence the longer the plasma retention time. Another chemical property is the C2/C6 ratio which is generally omitted from the product name (Fig. 11.3). It is the ratio of hydroxyethyl substitution at C2 and C6 carbon atoms of glucose subunit [1]. Greater hydroxyethylation at C2 inhibits degradation and hence a higher ratio leads to longer plasma retention. However, longer persistence in plasma may not necessarily mean a better volume effect. Newer or third-generation HES solutions have lower MS and MW resulting in more rapid metabolism and clearance and fewer adverse effects without loss of efficacy. Finally, the carrier solution can influence the adverse effects of some HES solutions. Different combinations of these three parameters account for a wide variety of commercially available products as depicted in Table 11.1.

In total, 30 to 40% of HES is eliminated renally and the remaining may be stored in tissues. Being a polydisperse solution, the smallest particles (< 60–70 kDa) are quickly

Table 11.1 Available HES solutions and composition

Parameter.	Types available	Effect
Concentration	6%,10%	Iso-oncotic, hyperoncotic
Molecular weight (MW)	130, 200, 450, 600, 670	Not significant
Molecular substitution (MS)	0.4, 0.5, 0.6, 0.7	Plasma retention time, adverse effects
C2/C6 ratio	4.5:1, 5:1, 9:1, 6:1, 3:1	
Carrier solution	Normal saline, balanced solutions	Adverse effects, acid–base status

excreted. Larger molecules are first broken down by alpha-amylase into smaller fragments before getting excreted renally. HES molecules are also phagocytosed by the reticuloendothelial system and may be found in the liver, spleen, kidneys, and bone marrow even after several years. Its deposition in cutaneous nerves is the cause of pruritus that may be debilitating and quite often long-lasting. Similarly, deposition in renal tubular cells is the cause of osmotic nephrosis like lesions [2].

Is Hydroxyethyl Starch Beneficial?

In the past, it was thought that colloids are 3–4 times more effective than crystalloids for restoring intravascular volume. This assumption was based on Starling's equation which states that maintenance of intravascular volume depends on the balance between plasma oncotic pressures and hydrostatic pressure. More recently, Starling's principle has been challenged after the discovery of the subendothelial glycocalyx layer and a revised Starling's equation has been proposed (described in greater detail in Chap. 2) [3]. In the 6S trial, the ratio of crystalloid to colloid to achieve the similar hemodynamic goal was 1.06 [4]. In the CHEST trial, the similar ratio was 1.17 [5]. Overall, resuscitation with HES requires somewhat less volume of fluid compared to crystalloid. But the benefit of this lesser volume requirement on patient outcomes remains less clear. In contrast, the association of HES with several adverse effects like renal injury, bleeding, pruritus, and allergic reactions is well established. In the following sections, we shall discuss available evidence from clinical trials on HES.

Evidence in Critically Ill Patients

Three large multicentre investigator-initiated randomized controlled trials (RCTs) demonstrated increased renal failure associated with starches in critically ill and septic patients [4, 5, 6]. In the VISEP trial,10% HES (200/0.5) in normal saline as the carrier solution was compared with lactated Ringer's solution for resuscitation of patients with severe sepsis

[6]. The trial was terminated after enrolling 600 patients as there was a trend towards increased 90-day mortality in the HES group. As expected, the total fluid required was less in HES group. There was a trend towards increased 28-day mortality (primary outcome) in the HES group, but it did not reach statistical significance. Higher cumulative doses of HES was clearly associated with an increase in 90-day mortality. Other secondary outcome measures like the incidence of acute kidney injury (AKI), the need for renal replacement therapy (RRT), and the need for red blood cell transfusion were significantly higher in the HES group. The trial was criticized for its two-by-two factorial (patients were simultaneously randomized for tight vs. conventional glucose control arm) and open-label design, use of more harmful pentastarch, and use of 0.9% saline as the carrier which may itself cause renal injury.

In the 6S trial, 798 patients with severe sepsis were randomized to receive either 6% HES (130/0.42) in Ringer's acetate or Ringer's acetate as resuscitation fluid [4]. The primary outcome, a composite of death or dependence on RRT at 90 days, was significantly higher in the HES group. Compared to Ringer's acetate, patients in the HES group also had significantly higher mortality at 90 days (51% vs. 43%). A significantly higher percentage of patients in the HES group required RRT during study period (22% vs. 16%). RRT-free and hospital-free days at 90 days were significantly lower in the HES group. However, 28-day mortality and the incidence of severe bleeding or allergic reactions were not different between the two groups. In the pre-specified subgroup analysis, the deleterious effects of HES were significant only in patients with septic shock at enrolment.

The CHEST trial, the largest of the HES trials, randomized 7000 patients admitted to ICU requiring fluid resuscitation (unlike only severe sepsis patients included by the previous trials) to receive either 6% HES (130/0.4) in 0.9% saline or 0.9% saline [5]. Primary outcome, i.e. mortality at 90 days, was not different between the HES group and the saline group (18% vs. 17%). However, more patients in the HES group had worsened renal outcome (higher RIFLE-R and RIFLE-I class but similar RIFLE-F class) and required RRT (7% vs. 5.8%). Interestingly, the incidence of new cardiovascular failure during study period was lower in the HES group. Patients in the HES group also received less study or non-study fluid, and the positive net fluid balance was significantly lower in the HES group compared to saline (921 ml vs. 982 ml).

Some experts argue that the aforementioned trials lacked a rational protocol for fluid therapy. Indication for fluid therapy included static parameters like central venous pressure (CVP) and none of these trials used dynamic parameters for fluid responsiveness (described in more detail in Chap. 5). Randomization happened late after ICU admission, possibly in the 'stabilization' phase of fluid therapy, missing the early 'resuscitation' phase (see ROSE concept described in Chap. 25). This is illustrated in Fig. 11.4. This is supported by the fact that mean CVP was 12 mmHg in VISEP and about 9 mmHg in the CHEST trial at baseline. About 40% of patients in both groups of the 6S trial had already received between 500 ml and 700 ml synthetic colloids prior to randomization, and in the VISEP trial patients had received a median of 2 litres of crystalloids and 850 ml of colloids
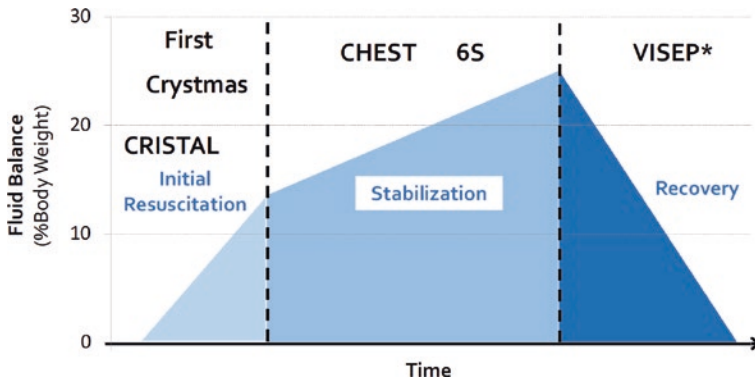
Fig. 11.4 Timeline vs. fluid balance expressed as a percentage of body weight. In the VISEP study, colloids were still administered late in the course of the disease

in 12 hours preceding randomization. Besides, resuscitation fluids could be administered from 21 to 90 days after randomization [4, 5, 6]. Thus, these trials might have ended up administering HES to 'non-hypovolemic' patients who should not have received fluids in the first place.

In the multicentre CRISTAL trial, 2857 patients of hypovolemic shock were randomized to receive either colloid (HES and gelatins, dextrans, or 4% or 20% of albumin) or crystalloid (isotonic or hypertonic saline or Ringer's lactate solution) for all fluid interventions other than fluid maintenance throughout the ICU stay [7]. The primary outcome (28-day mortality) was not different between the two groups. However, 90-day mortality and the use of RRT were significantly lower and mechanical ventilation−/vasopressor-free days at day 28 were significantly higher in the colloid group. The biggest strength of the trial was that it included patients in the very early phase of disease process. HES was given only on days zero to two of ICU admission and the median cumulative dose of HES was only 1500 ml, much less than in trials just described. However, the trial had its own flaws that cannot be ignored. Clinicians were free to use the colloid of their choice including HES, albumin, or gelatins, the trial was open-label, the recruitment period lasted unusually long (nine years), and like other trials subjects received substantial amounts of colloids before randomization.

To conclude evidence does exist for harm from the use of HES in critically ill and septic patients. Additional research is needed to establish or refute the role of 'early and limited' use of HES in 'initial' resuscitation of critically ill patients. Till that time, it is reasonable to avoid the use of HES for resuscitation of critically ill patients (especially patients with sepsis).

The importance for attention to detail is exemplified by the fact that commentaries in scientific journals and lectures at scientific meetings dealing with the major fluid trials often cite information only contained in the appendices of the original publications. Given the frequent emotional nature of the debate on this subject, this phenomenon might

ironically be termed 'appendicitis' [8]. The appendices are indeed necessary for accurate interpretation of data. The population, intervention, comparator, and outcome (PICO) method was applied on the two highly cited 6S and CHEST trials on fluid therapy in critically ill patients. The analysis shows that, going over all PICO criteria, the main text of both publications provide insufficient information (Table 11.2).

Table 11.2 Analysis of the 6S and CHEST trials using the population, intervention, comparator, and outcome (PICO) method

Patients	6S	CHEST
N	804	7000
Setting	ICU, Scandinavia	ICU, Australia and New Zealand
Inclusion criteria	Patients requiring fluid resuscitation in the ICU fulfilling the criteria of severe sepsis during the preceding 24 hours. Severe sepsis (100%). Definition of severe sepsis: Sepsis (focus of infection and at least two SIRS criteria) and at least one organ failure. Excluded were patients with intracranial haemorrhage or renal replacement therapy	Patients requiring fluid resuscitation over and above that required for maintenance. Hypovolaemia in medical and surgical ICU patients; sepsis in 29.2% and 28.4% of patients, respectively. Excluded were patients after cardiac surgery or with intracranial haemorrhage
Age and sex	66–67 years; 60–61% male	63 years; 60% male
Illness severity at baseline	Median SAPS II score 50 and 51, respectively; mechanical ventilation in 60 and 61% of patients, respectively; acute kidney injury in 36 and 35% of patients, respectively	Apache II score 17; mechanical ventilation in 64.1 and 64.9% of patients, respectively; no patients with impending or current renal failure
Vital signs at baseline	'Shock' (mean arterial pressure < 70 mmHg, need for inopressors, or serum lactate > 4 mmol/L < 1 h before randomization), in 84% of patients. CVP 10 mmHg; ScvO2 75 and 73%, respectively; serum lactate 2.0 and 2.1 mmol/L, respectively; arterial hypertension in 39% of patient**s**	Heart rate 89 bpm; mean arterial pressure 74 mmHg; CVP 9.5 and 8.9 mmHg, respectively; serum lactate 2.1 and 2.0 mmol/L, respectively
Non-trial fluids before randomization	Median amounts of 3500 and 3000 mL in 96 and 97% of patients, respectively	Not specifically reported; included in 'day 0' = day of randomization. Excluded were patients having had received >1000 mL HES before screening
Blood products before randomization	Median amounts of 838 and 600 mL in 23 and 22% of patients, respectively	Not specifically reported; included in 'day 0' = day of randomization

(continued)

Table 11.2 (continued)

Patients	6S	CHEST
Synthetic colloids before randomization	Median amounts of 700 and 500 mL in 42% of patients, respectively	HES in 15% of patients
Time from admission to randomization	Medians of 3.7 and 4.0 h, respectively	Mean 10.9 ± 156.5 and 11.4 ± 165.4 h, respectively
Intervention	6S	CHEST
Fluid	6% HES with molecular weight of 130 kDa, and substitution ratio of 0.42. Na + 140 m Mol/L, K+ 4 mmol/L, ca++ 2.5 mmol/L, mg++ 1.0 mmol/L, cl- 118 mmol/L, malate 5 mmol/L, acetate 24.0 mmol/L	6% HES with molecular weight 130 kDa, and substitution ratio of 0.42. Na + 154 mmol/L, cl- 154 mmol/L
Indication	Hypovolaemia as perceived by clinical judgment	Hypovolaemia as perceived by clinical judgment +1 physiological criterion (i.e. heart rate > 90 bpm, systolic or mean arterial pressure < 100 or < 75 mmHg, respectively, CVP < 10 mmHg, PAOP < 12 mm hg, respiratory pressure variation > 5 mmHg, capillary refill time > 1 s, urine output 0.5) ml/kg)
Maximum dose and duration	33/ml/kg/d IBW, 90 days	50 ml/kg BW/d, 90 days
Comparator	6S	CHEST
Fluid	Na+ 145 mmol/L, K+ 4 mmol/L, Ca2+ 2.5 mmol/L, Mg2+ 1.0 mmol/L, cl- 127 mmol/L, malate 5 mmol/L, acetate 24 mmol/L	Na + 154 mmol/L, cl- 154 mmol/L
Outcomes	6S	CHEST
Primary outcome	Composite death or dependence on dialysis 90 days after randomization	All-cause mortality 90 days after randomization
Modified intension-to-treat analysis primary outcome	Dead at 90 days: HES vs. comparator, RR 1.17 (1.01–1.36), $p = 0.03$. Survival time censored at 90 days: $p = 0.07$	Death at 90 days: HES vs. comparator, RR 1.06 (0.96–1.18), $p = 0.26$. Survival time censored at 90 days: $p = 0.27$
Per-protocol analyses primary outcome	Death at 90 days: Per-protocol analysis 1: HES vs. comparator, RR 1.14 (0.97–1.34), $\boldsymbol{p = 0.12}$. Per-protocol analysis 2: HES vs. comparator, RR 1.16 (0.97–1.37), $p = 0.07$	Death at 90 days if sepsis at randomization: RR 1.07 (0.92–1.25), $p = 0.38$. Death at 90 days, adjusted: RR 1.05 (0.95–1.16), $p = 0.33$
Secondary outcome	Renal replacement therapy	Renal replacement therapy

Table 11.2 (continued)

Patients	6S	CHEST
Modified intension-to-treat analysis secondary outcome	HES vs. comparator: RR 1.35 (1.01–1.80), $p = 0.04$	HES vs. comparator: RR 1.21 (1.00–1.45), $p = 0.04$. Adjusted: RR 1.20 (1.00–1.44), $p = 0.05$
Trial fluid	Day 1: Median amount of 1500 mL Days 1–3: Median amount of 4000 mL	Day 1: Mean amount of approx. 480 and 570 mL, respectively. Days 0–3: 2104 and 2464 mL, respectively
ICU fluid balance	Median amounts 5452 and 4616 mL, respectively	Days 0–3: Mean amounts of approx. 3120 and 3340, respectively
Circulatory variables at 24 h after randomization	CVP 11 and 10 mmHg, respectively; ScvO2 75 and 73%, respectively; serum lactate 2.0 mmol/L	Heart rate 87 bpm; mean arterial pressure 81 mmHg; CVP approx. 10.5 and 11.5, respectively; serum lactate approx. 1.5 mmol/L

Bold text indicates information that is only available in the appendix or in the legend of figures. Adapted with permission from Priebe et al. According to the Open Access CC BY Licence 4.0 [8].

Perioperative Use of HES

The settings of trauma and surgery are different from that of septic shock as they are not associated with the disruption of capillary glycocalyx to as great an extent as sepsis, burn, or pancreatitis with probably less leaky capillaries. This may offer an advantage to colloids like HES, perhaps producing a similar haemodynamic effect (compared to crystalloid) with lesser volume. In fact, most perioperative studies examining the goal-directed therapy (GDT) approach to fluid therapy used colloids – specifically HES. The GDT approach involves the use of invasive haemodynamic monitoring and giving fluids to reach a predetermined goal, for example, a stroke volume variation (SVV) of less than 10%. HES was compared to crystalloids in a recent trial of the GDT approach to fluid management in elective abdominal surgery [9]. Total intraoperative fluid and net fluid balance were significantly lower in the HES group. The HES group also had significantly lower postoperative morbidity score and lower incidence of postoperative complications. Authors attributed the beneficial effect of HES to the decrease in total intraoperative fluid administered. No renal adverse effects were noted even on long-term (up to 1 year) follow-up of the patients [10]. However, two other smaller RCTs on abdominal surgery patients didn't find any benefit or harm associated with use of HES [11, 12]. In addition, several meta-analyses failed to suggest any difference in outcome either benefit or associated harm (including nephrotoxicity) [13, 14] .

To conclude, there is no evidence to suggest harm associated with the use of hydroxyethyl starch in perioperative settings. However, in the absence of definite benefit and substantial cost involved, the use of HES cannot be strongly recommended even in this setting.

Controversies and Restrictions on HES

Between the year 2008 and 2012, several large multicentre randomized controlled trials indicated that HES increased the risk of renal failure requiring renal replacement therapy and death in critically ill patients in general and septic patients in particular [4, 5, 6]. By 2012, investigations were initiated by the U.S. Food and Drug Administration (U.S. FDA) and European Medicines Agency (EMA) pertaining to the safety of HES. In October 2013, EMA concluded that HES should no longer be used in patients with sepsis or burn injury or in critically ill patients; however, it can be prescribed to patients with hypovolaemia due to acute blood loss if treatment with crystalloids was inadequate. HES could still be used in surgical and trauma patients. The EMA also stated that no more than 30 ml/kg of HES should be administered and kidney function of patients receiving HES should be monitored. The U.S. FDA also issued a black box warning regarding the use of HES in November 2013. It prohibited the use of HES in critically ill patients and patients with sepsis, severe liver disease, and pre-existing coagulopathy.

Based on the studies conducted by the agencies suggesting widespread non-compliance to restrictions imposed on the use of HES including its use in prohibited (critically ill, sepsis) settings, EMA initiated a proposal in 2017 to ban HES completely. However, several experts argued against the complete ban on HES. They felt that the complete ban is potentially hazardous as this would lead to unmet medical needs with scarce and costly alternatives (i.e. albumin) [15]. Afterwards, the proposal to completely withdraw HES was withheld by the European Commission and HES continued to be available with restrictions and warnings imposed since 2013. However, the final curtain may fall over HES as EMA's safety committee, PRAC, has recommended in February 2022 that the marketing authorizations for HES solutions for infusion should be suspended across the European Union. This was based on new results of an ongoing safety analysis which showed that HES solutions for infusion are still being used outside the recommendations included in the product information. The committee concluded that the further restrictions introduced in 2018 have not sufficiently ensured that the medicines are used safely and that HES solutions continue to be used in certain groups of patients in whom serious harm has been demonstrated.

Gelatins

Gelatins are polypeptides derived from bovine collagen. Gelatin particles are smaller than other synthetic colloids (average MW 35000 Da) and therefore have a shorter clinical effect. Commonly available gelatin products are urea cross-linked (e.g. Haemaccel, originally marketed by Hoechst AG) and succinylated or modified fluid gelatins (e.g. Gelofusine, B. Braun Medical). The capacity of gelatin for plasma expansion, expressed by a mean crystalloid to colloid ratio of 1.4, is also not different from other colloids.

In a recent meta-analysis, including both randomized and non-randomized animal and human trials, comparing gelatin with crystalloids and albumin found that gelatin is associated with an increase in the risk of anaphylaxis (more than threefold), AKI, need for RRT, and need for blood transfusion [16]. There was also a trend towards increased mortality in the gelatin group though not statistically significant. However, a recent Cochrane systematic review failed to substantiate these findings [17]. Results of an ongoing trial on gelatin are awaited [18].

Gelatins are not approved for use by the U.S. FDA since 1978 due to its association with deranged coagulation parameters and prolonged bleeding time. Concerns over adverse effects, doubtful benefits, and short clinical effects lead several guidelines (including Surviving Sepsis Campaign) to recommend crystalloids over gelatins for fluid resuscitation.

Dextrans

Dextrans are a mixture of glucose polymers of various sizes. They are derived from the bacteria named *Leuconostoc mesenteroides* and have an average MWs of 40 kDa and 70 kDa. The formulations commonly available are 10% dextran-40 and 6% dextran-70. Following intravenous administration, dextran is almost exclusively eliminated by the kidneys except for a small fraction eliminated via the gastrointestinal tract. The length of time that dextran stays in the intravascular compartment is dependent on particle size. Approximately 60% to 70% of dextran-40 is cleared within 5 h. Dextran-70 has a duration of action of 6–8 h [19].

Dextrans are used to improve blood rheologic properties and for decreasing blood viscosity and indirectly to improve microcirculatory flow after vascular surgery. There is little evidence to support dextran as a resuscitation fluid. Moreover, dextrans cause more anaphylactic reactions than gelatins or starches and their use is also associated with renal failure and impaired coagulation.

Case Vignette
The patient in the case vignette is in septic shock (due to hospital-acquired pneumonia), and fluid resuscitation is indicated in view of hypotension and poor perfusion. Though giving a bolus of HES may lead to faster resolution with lesser volume, it now becomes clear that this leads to worse outcomes as strong evidence exists that the use of HES in sepsis may lead to kidney injury and increased mortality. Both the EMA and U.S. FDA forbid the use of HES in this setting. The case is more or less similar for other synthetic colloids. Balanced crystalloids remain the fluid of choice in septic shock, and if the need to use a colloid is inevitable albumin remains an option, especially at a later stage.

Conclusion

On May 24, 2022, the European Commission issued a legal decision confirming the suspension of the marketing authorizations of HES solutions for infusion. If necessary for public health reasons, individual EU member states may delay the suspension for no longer than 18 months and keep HES solutions on the market, subject to agreed risk minimization measures. Outside of the EU, as of now, the use of HES and other synthetic colloids should be restricted to resuscitation in perioperative setting or maybe in trauma settings in limited volumes (30 ml/kg) and with extreme caution.

Take-Home Messages
- The natural colloid albumin and several synthetic colloids are at the disposal of the acute care physician.
- Though marginally lesser volume of colloids produces similar hemodynamic effect, it has not resulted in any outcome benefit in clinical trials.
- The synthetic colloid HES is associated with renal failure and increased use of renal replacement therapy in critically ill and septic patients and its use remains restricted by several regulatory authorities across the world.
- HES solutions cannot be used in patients with sepsis, burns, and (acute) kidney injury and have recently been suspended in the ICU.
- Use of synthetic colloids in perioperative patients is unsafe as strong evidence showing their superiority over crystalloids is lacking.
- When given (outside the ICU) in the peri- and postoperative phase, the dose should be limited to 30 ml/kg.

References

1. Jung F, Koscielny J, Mrowietz C, Förster H, Schimetta W, Kiesewetter H, Wenzel E. The effect of molecular structure of hydroxyethyl starch on the elimination kinetics and fluidity of blood in human volunteers. Arzneimittelforschung. 1993;43:99–105.
2. Dickenmann M, Oettl T, Mihatsch MJ. Osmotic nephrosis: acute kidney injury with accumulation of proximal tubular lysosomes due to administration of exogenous solutes. Am J Kidney Dis. 2008;51(3):491–503.
3. Levick JR, Michel CC. Microvascular fluid exchange and the revised starling principle. Cardiovasc Res. 2010;87(2):198–210.
4. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367:124–34.
5. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367:1901–11.
6. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358:125–39.

7. Annane D, Siami S, Jaber S, Martin C, Elatrous S, Declère AD, et al. Effects of fl uid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA. 2013;310(17):1809–17.

8. Priebe HJ, Malbrain ML, Elbers P. The great fluid debate: methodology, physiology and appendicitis. Anaesthesiol Intensive Ther. 2015;47(5):437–40.

9. Joosten A, Delaporte A, Ickx B, Touihri K, Stany I, Barvais L, et al. Crystalloid versus colloid for intraoperative goal-directed fluid therapy using a closed-loop system: a randomized, double-blinded, controlled trial in major abdominal surgery. Anesthesiology. 2018;128(1):55–66.

10. Joosten A, Delaporte A, Mortier J, Ickx B, Van Obbergh L, Vincent JL, et al. Long-term impact of crystalloid versus colloid solutions on renal function and disability-free survival after major abdominal surgery. Anesthesiology. 2019;130(2):227–36.

11. Yates DR, Davies SJ, Milner HE, Wilson RJ. Crystalloid or colloid for goal-directed fluid therapy in colorectal surgery. Br J Anaesth. 2014;112:281–9.

12. Feldheiser A, Pavlova V, Bonomo T, Jones A, Fotopoulou C, Sehouli J, Wernecke KD, Spies C. Balanced crystalloid compared with balanced colloid solution using a goal-directed haemodynamic algorithm. Br J Anaesth. 2013;110:231–40.

13. Raiman M, Mitchell CG, Biccard BM, Rodseth RN. Comparison of hydroxyethyl starch colloids with crystalloids for surgical patients: a systematic review and meta-analysis. Eur J Anaesthesiol. 2016;33(1):42–8.

14. Gillies MA, Habicher M, Jhanji S, Sander M, Mythen M, Hamilton M, Pearse RM. Incidence of postoperative death and acute kidney injury associated with i.v. 6% hydroxyethyl starch use: systematic review and meta-analysis. Br J Anaesth. 2014;112(1):25–34.

15. Annane D, Fuchs-Buder T, Zoellner C, Kaukonen M, Scheeren TWL. EMA recommendation to suspend HES is hazardous. Lancet. 2018;391:736–8.

16. Moeller C, Fleischmann C, Thomas-Rueddel D, Vlasakov V, Rochwerg B, Theurer P, et al. How safe is gelatin? A systematic review and meta-analysis of gelatin-containing plasma expanders vs crystalloids and albumin. J Crit Care. 2016;35:75–83.

17. Lewis SR, Pritchard MW, Evans DJ, Butler AR, Alderson P, Smith AF, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018;8:CD000567.

18. Marx G. Gelatin in ICU and sepsis (GENIUS). Available online at https://clinicaltrials.gov/ct2/show/NCT02715466

19. Svensén C, Hahn RG. Volume kinetics of ringer solution, dextran 70 and hypertonic saline in male volunteers. Anesthesiology. 1997;87:204–12.