The Dilemma for Using Hydroxyethyl Starch Solutions for Perioperative Fluid Management

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Abstract

Hydroxyethyl starch is a colloid plasma expander that has recently been restricted by the European Medicines Agency (EMA) following safety concerns in critically ill patients or in patients with sepsis (2013). The EMA restricted HES use in these patients but continues to allow its use in surgical and trauma patients who suffer from hypovolemia due to blood loss that cannot be corrected by crystalloids alone. Following drug utilisation studies which showed that HES continued to be used in patients with contraindications, EMA conducted a new revision and introduced new risk minimization measures in 2018 to reinforce existing restrictions. This narrative review explains the basis for initial approval of HES, the presumed action of HES as plasma expander, and the mechanisms of its adverse effects on coagulation and on extravascular tissue uptake, especially in the kidneys with resulting renal failure, and presents an overview of recent important studies with a focus on surgery and trauma. No definitive, large-scale randomized controlled trials with patient-relevant outcomes and long-term follow-up exist in this population. Existing studies provide no assurance of a lower risk of coagulopathy, mortality, or kidney failure than in other critically ill patients. There are sufficient data to suggest that HES has similar risks also in these patients and should therefore be avoided.

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Key Points

1. Colloid solutions are theoretically superior to crystalloids as plasma expansion fluids but in practice have failed to show a patient-relevant benefit.
2. The colloid hydroxyethyl starch (HES) has potentially severe side effects due to impairment of coagulation and extravascular uptake with resulting kidney or other organ failure.
3. Because HES was introduced in the 1970s before adequately designed clinical phase I-III trials were mandatory, no evidence from randomized controlled trials (RCTs) was generated until investigator-initiated trials in critical care and sepsis revealed dose-dependent adverse HES effects on the kidney and coagulation system.
4. The available studies in surgical patients and patients with severe trauma provide no assurance that these patients have a lower risk of adverse events than other critically ill patients.
5. The European Medicines Agency (EMA) decision to restrict HES use only in critical care and sepsis and to allow its continued use in surgery and trauma is controversial and creates a dilemma, because treating acute blood loss in surgical and trauma patients with a substance that has no benefit but increases risks such as coagulopathy or renal failure seems paradoxical.

Introduction

Current Situation

Hydroxyethyl starch (HES) is a colloid plasma expander that is licensed to treat clinical states of hypovolemia and used in a variety of clinical settings. Based on two reviews, the European Commission implemented a decision in 2013 that because of the risk of kidney injury and mortality, HES solutions should no longer be used in patients with sepsis or burn injuries or in critically ill patients, and restricted the use of HES to the treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient (Box 12.1) [1].

Box 12.1 Restrictions to HES use issued by EMA 2013, confirmed in 2018: *Contraindications, warnings, and restrictions to HES use issued by EMA 2013* [2]

Contraindications

- Sepsis
- Burns
- Impaired renal function or renal replacement therapy
- Intracranial or cerebral hemorrhage

– Critically ill patients
– Hyperhydration
– Lung edema
– Dehydratation
– Severe coagulopathy
– Severe impairment of liver function

Restrictions

– HES solutions should only be used for the treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient.
– There is a lack of robust long-term safety data in patients undergoing surgical procedures and in patients with trauma. The expected benefit of treatment should be carefully weighed against the uncertainties with regard to long-term safety, and other available treatment options should be considered.
– HES solutions should be used at the lowest effective dose for the shortest period of time. Treatment should be guided by continuous hemodynamic monitoring so that the infusion is stopped as soon as appropriate hemodynamic goals have been achieved.
– HES solutions are now contraindicated in patients with renal impairment or renal replacement therapy. The use of HES must be discontinued at the first sign of renal injury. An increased need for renal replacement therapy has been reported up to 90 days after HES administration. Patients' kidney function should be monitored after HES administration.
– HES solutions are contraindicated in severe coagulopathy. HES solutions should be discontinued at the first sign of coagulopathy. Blood coagulation parameters should be monitored carefully in case of repeated administration.

New risk minimization measures introduced in 2018

• Implementation of a controlled access program by manufacturing companies. Only accredited hospitals/centres will be supplied with these medicines. The accreditation would require that relevant healthcare professionals who prescribe or administer them receive mandatory training on their safe and effective use.
• Warning and reminders in the packaging insert
• Direct letter to healthcare professionals
• Request to manufacturers to conduct studies to check that only patients who should be treated with these medicines are receiving them. These studies are in addition to ongoing studies on benefits and risks of HES solutions in patients with trauma and those undergoing elective surgery

The European Commission also issued contraindications and warnings for the use of HES outside the intensive care unit (ICU). HES solutions are now contraindicated in patients with renal impairment or renal replacement therapy, severe liver function impairment, and in severe coagulopathy. The expected benefit of treatment should be carefully weighed against the uncertainties with regard to long-term safety, and other available treatment options should be considered. In order to minimize potential risks in these patients, HES solutions should be used at the lowest effective dose, not be used for more than 24 h, and patients' kidney function should be monitored after HES administration. The use of HES must be discontinued at the first sign of renal injury. Additional post-marketing studies are required in patients with trauma and in elective surgery [2]. Recommendations by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) were endorsed by the majority of PRAC; however, there was substantial controversy. Fourteen of 36 members disagreed with the majority decision, voted for complete suspension given the lack of proven clinical benefit and the absence of positive evidence to provide reassurance of safety evidence for harm in surgery or trauma (Box 12.2) [2].

In 2017, Public Citizen, a US-American nonprofit consumer advocacy organization with over 500,000 members, sent petition letters to the FDA and to EMA, requesting the ban of HES. In 2017, EMA initiated a third review process triggered by a request from Swedish regulators, citing drug use studies suggesting that the medicines continue to be used in prohibited populations. Based on all available evidence from stakeholders, the EMA PRAC Committee recommended to suspend HES. This recommendation was endorsed by the regulatory body representing the European Union (CMDh). However, some EU member states requested further revision, arguing concerns about unmet medical need and unregarded scientific or technical questions, inducing the EC to refer the recommendation back to the CMDh. The revised CMDh recommendation—restriction and new risk minimization measures (Box 12.1) - were issued in July 2018.

Box 12.2 Divergent Statement by the EMA PRAC Committee

Divergent Statement by the EMA PRAC Committee in 2013 [2]

- Without evidence to provide reassurance that patients will not be exposed to increased risk of mortality and renal injury by use of HES, and given the lack of data supporting a clinically relevant benefit, suspension of marketing authorizations for HES products in all patient populations remains appropriate to protect public health.
- The mechanism underlying the risks of renal injury and mortality observed with HES is not well understood, and therefore these should be considered to be potential risks in all patient groups.
- The available studies in elective surgery and trauma cannot provide reassurance of a lower risk than in septic and critically ill patients, or indeed exclude such a risk.

- There is an overlap between those patient groups where the benefit–risk balance of HES is judged to be negative (septic and critically ill patients), and the patients who will receive HES under the revised indication allowing use in patients with hypovolemia due to acute bleeding (e.g., including the trauma and perioperative settings).
- There is very limited evidence on the benefits and risks of hydroxethyl starch solutions for use in elective surgery and trauma. There is some evidence that the volume-sparing effect of HES relative to crystalloid solutions is less than 3- to 4-fold, and may be around 1.8-fold in some types of surgery. The data evaluating benefit in the perioperative setting and trauma setting do not adequately support a clinically relevant beneficial effect for HES.
- Alternative treatments are available in the form of crystalloids, and high-quality care is possible without the use of HES according to a survey of 391 ICUs worldwide conducted in 2010 [3], which showed no use of HES in the United States or Australia.
- The ability of the proposed risk minimization measures to sufficiently minimize the risks of HES is a concern. Data are lacking to identify an appropriate maximum dose, and expert advice is that there is no absolute "safe" lower dose below which there is no risk associated with HES administration. The recommendation to monitor renal function in patients for at least 90 days may not be an effective measure to minimize the risk of renal injury in all patients, as detection of worsening of renal function by monitoring may not be practical in patients who are discharged shortly after receiving HES. Furthermore, in emergency settings, it may be particularly difficult to evaluate patients for contraindications.

Approval of Hydroxyethyl Starch in 1971

HES first received regulatory approval for use in the United States in 1971. This was before regulatory requirements as we know them today were put into place, which call for efficacy and safety data from phase I, II, and III trials; these were installed only after 1978 following workup of the thalidomide disaster [4, 5]. According to the legislation current at that time, HES licensure was based on efficacy data—mainly systolic blood pressure measurements—from several small, uncontrolled observations of a total of 315 patients and volunteers with observation periods of 24 h or less [6]. Subsequently, modified HES solutions, for instance, the so-called "modern" tetrastarch HES 130/0.4, were granted regulatory approval based predominantly on data from the initial approval [7]. Although new HES products were regularly marketed as "improved" with "less side effects" [8], evidence for this assumption from large-scale randomized controlled trials with crystalloid control fluids was not provided [9, 10].

Dose Limits

The dose limits for HES are set arbitrarily and are not the results of dose-finding studies with adequate comparators. Initially, daily dose limits were set at 20 ml/kg in analogy to the dose limit for dextran, a synthetic colloid already in use when HES was introduced, with which HES was found to share the side effect of dose-dependent prolonged bleeding [7]. In 1999, after the Pharmacovigilance Francaise reported fatal bleeding complications after HES 200/0.6 in patients with subarachnoidal hemorrhage, a cumulative dose limit of 80 ml/kg was introduced in France for HES 200/0.6 and daily control of coagulation parameters was recommended for other HES solutions if they were administered over 4 days or in excess of 80 ml/kg [11, 12]. The dose threshold for 6% HES 200/0.5 in Europe was 33 ml/kg/day. For the new, supposedly "safer" HES 130/0.4, this ceiling was raised to 50 ml/kg, based on the outcomes of a volume-replacement study (HS-13-24-DE) that was never published [7]. In 2008, a pooled analysis [13] on blood loss comparing HES 200/0.5 and the new HES 130/0.4 revealed that the HS-13-24-DE study had identified more blood loss after the use of the newer starch, which may have been the reason not to publish the results. Following the EMA review in 2013, the daily dose limit for starches was reset to 30 ml/kg. Of note, no safe HES dose is known. The Australian Crystalloid versus Hydroxyethyl Starch Trial (CHEST) identified a significantly increased occurrence of renal failure requiring renal replacement therapy (RRT) at a daily average dose of 526 ± 425 ml HES 130/0.4, which corresponds to 7.5 ml/kg for a 70 kg patient [14].

Pharmacokinetic Properties of Hydroxyethyl Starch

Hydroxyethyl starches are carbohydrate polymers. Because unmodified starches are rapidly degraded and insoluble at neutral pH, HES solutions are modified by hydroxyethylation that takes place at the carbon atoms of the glucose subunit of the starch molecule, predominantly at the C2 and C6 carbon atoms, and replaces the hydroxyl groups at the C-atoms by hydroxyethyl groups. This achieves a greater spread of the glucose polymer branches, increases solubility, and decreases intravascular cleavage by the enzyme alpha-amylase [15, 16]. HES solutions are thus classified by their degree of molar substitution (DS), which describes the proportion of hydroxyethylation at the C atoms of the glucose unit and can range from 0.4 (40%) to 0.7 (70%). Accordingly, HES solutions are known as tetrastarches (DS 0.4), pentastarches (DS 0.5), hexastarches (DS 0.6), and hetastarches (DS 0.7).

HES solutions are also described by their mean molecular weight. Different HES solutions are classified by the weight average, which is reported in kiloDaltons (Mw) and can range between 70 and 670. There are currently about 30 different HES solutions on the market worldwide. Of note, HES are polydisperse solutions, meaning that they contain a mixture of molecules of different molecular weights. This is caused by the already existing molecular weight distribution of the starting material (starch) and the cleavage of glycosidic bonds during the hydrolysis process.

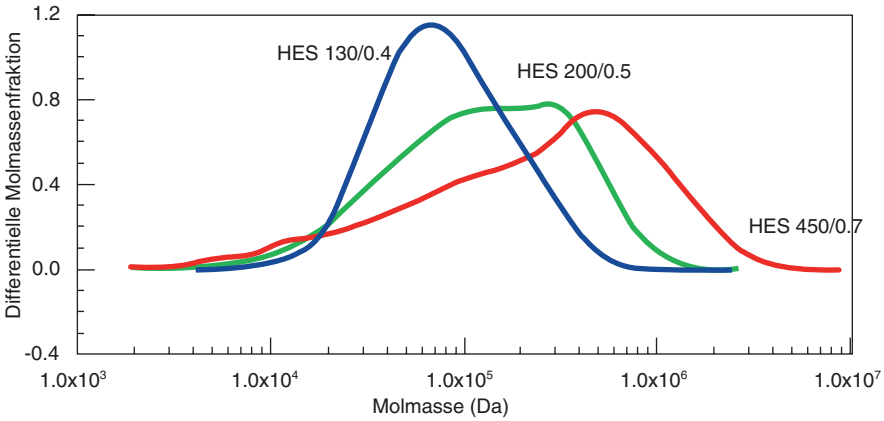

Fig. 12.1 Molecular size distribution in serum of rats after application of different HES solutions. This figure shows the distribution of molecular size in different HES solutions. All HES solutions are polydisperse and contain molecules of different sizes. The *x*-axis shows the molecular weights in Daltons, the *y*-axis shows the differential fraction of molecular sizes among each solution (Reprinted with permission from Wagenblast [16])

As Fig. 12.1 shows, all HES solutions contain varying molecular sizes from very small to very large molecules in the range of several hundreds of kiloDaltons. Thus, even in solutions with different means of molecular weights, for instance, the so-called "modern" tetrastarch solution (HES 130/0.4) and pentastarch (HES 200/0.5), the molecular weight distribution curves that describe the range of molecular sizes contained in the solutions may be quite similar [17]. These facts may explain that adverse effects of HES solutions are class effects that do not differ substantially between single solutions.

The Metabolic Fate of the Hydroxyethyl Starch Molecule

The metabolic fate of HES solutions is not well described. After infusion, HES molecules are cleared from plasma by renal elimination and tissue uptake [15, 18–20]. HES is not excreted through the feces [21]. Since only 40–65% of an infused dose could be recovered in the urine in humans, the remainder of the dose may be stored in the body [22]. Indeed, between 30 and 40% of administered HES solutions, regardless of their pharmacokinetic properties, are taken up transiently by tissue [23]. A recent systematic review included clinical studies that reported cumulative urinary excretion of HES over 24 h after infusions and plasma HES concentration at 24 h. Tissue uptake was computed as the difference between the infused dose and the sum of urinary excretion and residual plasma HES at 24 h and results were stratified by different HES solutions. Twenty-five clinical studies totaling 287 subjects were included. The 24-h tissue uptake was similar between different HES solutions, with 42.3% (95% confidence interval [CI] 39.6, 45.0) for low-molecular-weight HES (≤200 kDa) and 24.6% (CI 17.8, 31.4) for high-molecular-weight HES (>200 kDa) [24].

The uptake of HES into cells may alter their function. In cell cultures of human proximal tubular cells, application of HES 130/0.4 led to the ingestion of HES molecules into the cells and subsequent decrease of cell viability, which was not seen after application of crystalloids or low-dose albumin [25]. HES has been found in tissues of the reticuloendothelial system such as in kidneys, liver, spleen, and bone marrow. In 1998, Ginz et al. reported a case of a patient with sepsis who was treated with dextran (Mw 40,000 and 70,000 Da) and HES (Mw 450,000 Da, DS 0.7) for 5 weeks. Autopsy showed large colloid mass inclusions in parenchymal and reticuloendothelial cells of liver, lung, kidney, and spleen with altered organ morphology [26]. HES uptake has been reported in a wide variety of cell types, such as monocytes, macrophages, endothelium, renal epithelial cells, parenchymal liver cells, Schwann cells, and keratinocytes [24, 27], as well as in cells of the placenta [28]. HES storage in cutaneous nerve cells may cause severe and lasting pruritus [29–31].

Although HES is commonly administered to patients with severe and critical illness, most data on tissue uptake stem from studies in healthy volunteers. We have only scarce data on the metabolism of HES in severely sick patients and the long-term effects of HES tissue storage in patients. HES deposits are detectable for many months or years. Sirtl et al. studied 26 patients for up to 7 years after HES administration. Biopsies of the liver, muscle, spleen, intestine, or skin were studied using light and electron microscopy and immunohistochemistry. HES storage was detectable in all biopsies and was dose-dependent, decreased in all organs with time, and was greater in patients suffering from pruritus [32]. HES uptake into renal tubular cells appears as “osmotic nephrosis-like lesions” [33]. Pillebout et al. performed renal biopsies in patients who developed renal failure after liver transplantation. The authors found osmotic nephrotic lesions indicative of HES uptake as long as 10 years after its administration [34].

Transvascular Fluid Exchange and the Updated Starling Model

Colloids have long been believed to be more effective to achieve intravascular fluid expansion than crystalloids, based on the original model initially developed by Ernest Starling from experiments on the isolated hind limb of a dog. The original Starling model described fluid exchange as the product of differences between intra- and extracellular oncotic pressures and capillary permeability. However, the traditional form of Starling’s principle has to be modified in light of insights into the role of interstitial fluid pressures and the lymphatic system, the recognition of the glycocalyx as the semipermeable layer of endothelium, local epithelial secretions in some specialized regions (e.g., kidney, intestinal mucosa), and standing plasma protein gradients within the intercellular cleft of continuous capillaries and around fenestrations. A more current explanation uses a two-pore system model where relatively small increases in large pore numbers dramatically increase fluid exchange during acute inflammation [35]. Colloid supporters have upheld that the demonstrated ineffectiveness of biophysical colloid therapy is due to damaged glycocalyx or capillary leakage, but according to new findings from fluid physiology—as Thomas Woodcock et al. have nicely explained in their well-researched paper on the glycocalyx model

of transvascular fluid exchange (see Chap. 8 of this book) [36]—colloid therapy is ineffective because the colloid osmotic pressure of plasma restricts but does not reverse the transendothelial fluid flux from capillary to interstitium. In particular, reabsorption of filtered fluid at the venous end of a nonfenestrated capillary is essentially insignificant for clinical considerations [37].

Hemodynamic Effects

Meta-analyses performed by the Cochrane Collaboration have consistently found that resuscitation with colloids is not associated with an improvement in survival, compared to resuscitation with crystalloids, in patients with trauma, burns, or following surgery [38]. These reviews have challenged the routine use of colloids, which are not beneficial but considerably more expensive than crystalloids. However, colloids and in particular starches were the preferred fluids in critical care [3]. The traditional understanding and one of the arguments used in favor of starches was that they were superior to crystalloids in increasing myocardial preload and intravascular volume. Indeed, colloids achieve a more rapid improvement in the hematocrit than crystalloids but this effect is transient [39]. The widely held belief that about fourfold or even higher volumes of crystalloid than colloid fluids are required to achieve hemodynamic stabilization has been challenged in the last years by large-scale fluid studies that compared crystalloid and colloid resuscitation. They showed crystalloid-to-colloid ratios between 1 and 1.45 (Fig. 12.2) [14, 39–45]. Thus, the volume-sparing effect of colloids is considerably lower than believed. A

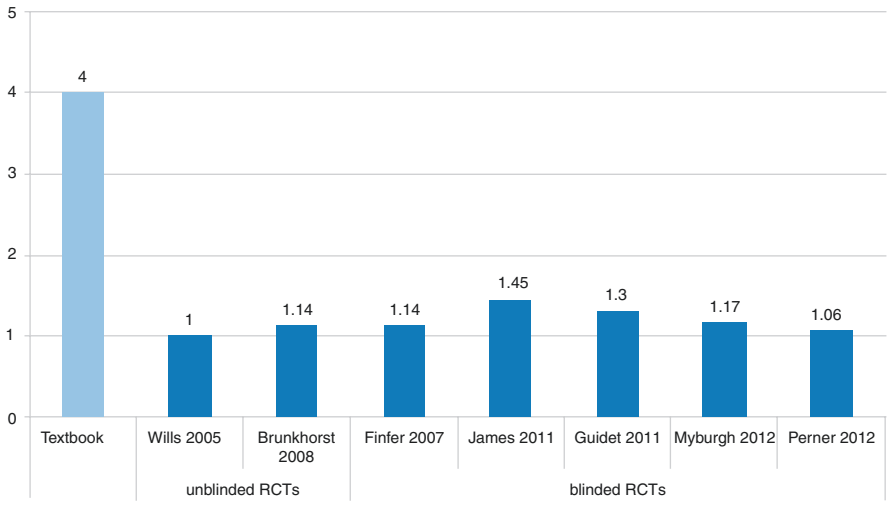

Fig. 12.2 Crystalloid-to-colloid ratios. While textbook knowledge based on theoretical arguments postulates a crystalloid-to-colloid ratio of 4 or higher, recent RCTs, among them five where study personnel were blinded to the nature of the administered fluid, found ratios between 1 and 1.45. The *y*-axis shows the ratio of crystalloid-to-colloid volumes that were administered to achieve preset hemodynamic endpoints in the respective studies [14, 39–45]

recent meta-analysis assessed the crystalloid/colloid ratio in studies comparing (any) crystalloid with (any) colloid in all types of patients. Twenty-four studies had sufficient data for meta-analysis. The crystalloid/colloid ratio across all the studies included in the meta-analysis was 1.5 (95% confidence interval [CI], 1.36–1.65) with marked heterogeneity among studies (I^2 = 94%). The authors stated that the crystalloid/colloid ratio had decreased over the years, but the main reasons behind the high heterogeneity among studies remain unclear [46].

The effect of colloids may be mitigated in critically ill or septic patients who may have increased capillary permeability. What is the fluid ratio in surgical patients? The effect of HES on cardiac surgical patients was prospectively assessed in a before-and-after study by Bayer et al., who compared a treatment period with HES against a treatment period in which only crystalloids were used; this study included 2137 patients in the HES period and 2017 in the crystalloid period. Shock reversal was similar in both periods: Time to vasopressor cessation, normalization of serum lactate, and mean arterial pressure did not differ among groups. Total fluid requirement was 163 ml/kg in the HES period and 224 ml/kg in the crystalloid period (ratio 1.37) with a higher fluid intake in the crystalloid group only during the first 20 h [47].

Do Patients Benefit from Hydroxyethyl Starch?

Does the advantage of requiring somewhat less fluids to achieve similar hemodynamic outcomes confer a patient-relevant advantage in clinical trials? No trial could yet show that patients benefitted from fluid resuscitation with HES, as observed consistently in the meta-analyses from the Cochrane Collaboration [38]. It is unclear how the presumed benefit of HES can be established. HES supporters [48] now argue that HES had not been given correctly in recent RCTs that showed negative effects after HES administration [14, 43] and that HES may still be beneficial if it were applied early, according to an algorithm, under observation of a maximum dose and in the absence of renal failure. The authors themselves concede that these arguments are speculative [48]. The discussion recalls similar arguments that were made to explain the negative findings from the first sepsis trials in France and Germany, suggesting that kidney failure might have been avoided by using newer starches and "watering the kidney" sufficiently with crystalloids [9].

To date, clinical trials have shown that HES is not beneficial in a variety of patient populations. The blinded RCT of 7000 ICU patients from the Australian and New Zealand Intensive Care Trials Group ANZICS found that 90-day mortality was not different (17% in the saline group vs. 18% in the HES 130/0.4 group) [14]. The recent large sepsis trials showed an excess mortality in the HES groups at 90 days [40, 43, 45] (discussed in more detail in the following section). In trauma, the first and blinded trial to compare HES with crystalloid showed excess mortality after 30 days, reported in a post hoc letter by the authors [41, 42]. Systematic reviews and meta-analyses of trials with surgical patients found no clinical benefit for patients receiving 6% HES solutions or alternative intravenous (IV) fluids (19 trials with

1567 patients) [49]. Hemodilution with HES was also not beneficial in indications outside critical care, for instance, in acute hearing loss [50], pre-eclampsia [51], postoperative nausea and vomiting [52], or postoperative fluid therapy to reduce surgical site infection [53]. Most recently, the FLASH multicenter randomized controlled trial, which assessed the effects of HES vs saline for fluid resuscitation in patients undergoing major abdominal surgery, found that the primary endpoint (a composite endpoint of death or major postoperative complications) occurred in 36% of patients (139/389) in the HES group vs 32% (125/386) in the saline group (absolute difference, 3.3%; 95% CI, −3.3% to 10.0%; P = .33) without significant difference but showed a trend favoring saline. Patients in the HES group received less study fluids on the day of surgery (median 500 mL) but had lower diuresis and a more positive fluid balance on day 2 [54].

Hydroxyethyl Starch Toxicity

Like other synthetic colloids, HES is associated with a range of adverse effects. The pathomechanisms of these effects are not fully explored. Bleeding impairment may result from interference with thrombocytes and coagulation factors [55, 56], while tissue storage resulting from the rapid accumulation of HES in tissues and macrophages [24] may be the most important mechanisms that influence morbidity and survival in susceptible patients in a dose-dependent manner. There has been some debate about whether molecular weight, substitution, or rather the cumulative dose plays a role and whether HES has different effects in surgical or trauma patients [8]. These questions will be addressed as follows.

Mortality

Critically ill and septic patients In 2008, the open-label Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial, which randomized septic patients to 10% HES 200/0.5 or Ringer's lactate, found a trend toward increased 90-day mortality in the HES group (41.0% vs. 33.9%, $P = 0.09$), with the rate of death being significantly increased among patients who received a higher dose of HES, as compared with those who received a lower dose (57.6% vs. 30.9%, $P < 0.001$) [40]. A subsequent blinded RCT with 804 septic patients by the Scandinavian Critical Care Trials Group compared HES 130/0.4 to Ringer's acetate and found an increased 90-day mortality rate in the HES group (51% vs. 43%, relative risk [RR], 1.17; CI 1.01–1.36; $P = 0.03$) [43]. The CHEST trial with 7000 ICU patients and a blinded comparison of HES 130/0.4 versus normal saline found that 18.0% in the HES group and 17.0% in the saline group died within 90 days (relative risk in the HES group, 1.06; CI 0.96–1.18; $P = 0.26$) [14].

The reason why these studies could show not only the lack of survival benefit, but also harmful effects after HES resuscitation was that these investigator-initiated trials had sufficiently large patient samples to detect effects in patient-relevant

outcomes such as renal failure or transfusion exposure. In addition, they had a long enough follow-up period of 90 days to detect effects that only become manifest after longer periods of time. When these trials were included in a meta-analysis by a Canadian group, which evaluated acutely ill patients from 28 HES solution trials, starches—regardless of degree of molar substitution or molecular weight—were associated with increased mortality among 10,290 patients (relative risk, 1.09; 95% CI, 1.2–1.17) and increased use of renal replacement therapy among 9258 patients (RR, 1.32; 95% CI, 1.15–1.50) [57].

Surgical and trauma patients In these patients, such large-scale RCTs have not yet been performed. Small studies not surprisingly are too small to detect an effect of HES therapy on ICU or mortality in populations where the given risk of mortality is low. However, even small studies may suggest harmful effects of HES on outcomes. One of the larger studies was performed by Skhirtladze et al., who randomized 240 patients undergoing elective colorectal surgery to receive up to 50 ml/kg per day of either 5% human albumin (HA), 6% HES 130/0.4, or Ringer's lactate (RL) as the main infusion fluid perioperatively. The 90-day mortality was 2.6% (2/76) in the HA group, 1.2% (1/81) in the HES group, and 0% (0/79) in the RL group [58]. There was also a significant difference in blood loss in favor of starch, which will be discussed later. Feldheiser et al. performed a double-blind RCT with a 90-day follow-up in 50 patients undergoing gynecological cancer who received either HES 130/0.4 or crystalloid; five deaths were reported in the HES group, while no subjects died in the crystalloid group ($P = 0.051$) [59]. James et al. performed a blinded RCT in 115 trauma patients [41]; 30-day mortality rates were 12/56 (21%) in the HES and 6/53 (11%) in the crystalloid group as explained in a letter by the authors [42]. In the FLASH trial, death at 14 days occured in 12/389 (3%) of patients receiving HES and in 6/386 (2%) of patients receiving saline [54].

Coagulopathy and Prolonged Bleeding

At the time HES was introduced in the 1970s, scientists were aware of the fact that synthetic colloids prolonged bleeding but the mechanisms were obscure. In 1975, Alexander performed a set of elegant experiments and could show that the hemostatic defect associated with the use of plasma substitutes such as dextran or HES is a form of induced von Willebrand disease or disseminated intravascular clotting, ensuing from precipitation and removal of von Willebrand factor, factors VIII and I, microcirculatory abnormality, and platelet malfunction [60]. A systematic review of the influence of tetrastarches on hemostasis as measured by viscoelastic device analysis found that HES 130/0.4 administration results in hypocoagulation characterized by the formation of a weaker and smaller clot [61].

In susceptible patients, administration of HES can lead to potentially fatal bleeding. In France, HES 200/0.6 received a warning label [11] after a pharmacovigilance study documented three cases of fatal cerebral hemorrhage among nine patients with subarachnoid hemorrhage and acquired von Willebrand syndrome

after HES exposure [12]. In the United States, the Food and Drug Administration (FDA) issued a warning label for HES in 2004 because of increased bleeding observed in cardiac surgical patients [62]. Evidence from several large-scale RCTs in critically ill and septic patients demonstrated that pentastarch as well as the new tetrastarch significantly increased the need for transfusion of blood products in these severely ill patients [14, 40, 43, 63].

Evidence from surgical trials is poor due to the lack of large-scale RCTs in this setting with the statistical power to detect differences in patient-relevant outcomes. However, published trials suggest increased blood loss and transfusion need after administration of HES. Skhirtladze et al. [58] compared the effects of 5% albumin, 6% HES 130/0.4, and Ringer's lactate on blood loss after cardiac surgery and found that 35% of RL patients required blood products, compared with 62% (HA) and 64% in the HES group ($P = 0.0003$). In the double-blind trial conducted by Yates et al., which compared 6% HES 130/0.4 with crystalloid in colorectal surgery, 20/84 (23.8%) of patients in the HES group received blood transfusions versus 10/88 (11.4%) of patients in the crystalloid group; that is, a doubling of events [64]. Rasmussen et al. randomized 16 patients to receive either 6% HES 130/0.4 or Ringer's lactate during major surgery; thrombelastography showed that HES dilution led to a reduced clot strength while blinded evaluation of blood loss was 2.2 l (range 0.5–5.0) in the HES versus 1.4 l (range 0.5–2.4) in the crystalloid group ($p < 0.038$) [65]. In a prospective, randomized, double-blinded study, Schramko et al. assigned 50 patients scheduled for complex cardiac surgery to receive either balanced 6% HES 130/0.42 or Ringer acetate solution for cardiopulmonary bypass (CPB) priming. Randomization was stopped prematurely after 35 randomized patients (19 in the HES and 16 in the Ringer groups) because of the published report where HES 130/0.42 was associated with impaired renal function. Effects on hemostasis and fluid balance were investigated. Patients in the HES group needed more blood and blood product transfusions [66]. A few other small RCTs that investigated the modern HES 130/0.4 found induced hypocoagulation [67–69] and increased the use of blood products [68], while other small RCTs described reduced transfusion after HES administration [70]. Overall, a recent meta-analysis on the impact of starches on blood loss in cardiac surgery found that HES in comparison to albumin increased blood loss, reoperation for bleeding, and blood product transfusion after cardiopulmonary bypass without evidence that these risks could be mitigated by lower molecular weight and substitution [71]. These findings are confirmed by the recent FLASH trials in abdominal surgery, where significantly more patients receiving HES than saline received transfusions during the surgical procedure (19% vs 12%; P = .003) [54].

Kidney Failure in Critically Ill and Mixed Populations

Renal impairment after HES may be due to a plurality of causes, including reabsorption of HES into proximal renal tubular cells, which lead to characteristic lesions called "osmotic nephrotic lesions" [33], or renal plugging due to hyperviscous

urine [72]. Huter et al. investigated HES-induced adverse effects on renal function using an isolated porcine renal perfusion model and crystalloid controls. They observed HES-induced impaired diuresis and sodium excretion and identified renal interstitial proliferation, macrophage infiltration, and tubular damage [73]. Neuhaus et al. found that application of HES 130/0.4, but not crystalloid, to cell-cultured human proximal renal tubular cells decreased cell viability significantly in a concentration-dependent manner [25]. Bruno et al. could show that these harmful effects on human proximal renal tubular cells correlated only with the total administered dose of HES molecules; molecular size, substitution, and origin of starch (cornstarch or potato starch) were not relevant [74]. Schick et al. induced sepsis in rats by cecal ligation and puncture and treated the animals with crystalloid or colloid solutions. After 24 h the kidneys of animals treated with HES or gelatin showed osmotic nephrotic lesions and an overall increased injury compared to kidney from animals treated with crystalloids [75].

Clinical reports of renal failure associated with HES administration were first noted in France in 1993 [76]. Subsequent observations noted a higher incidence of kidney transplant failure in donors resuscitated with HES [77]. This triggered an investigator-initiated prospective randomized trial published in 2001 that compared resuscitation with 6% HES against 3% gelatin and reported a significantly higher occurrence of acute kidney failure in the HES group [78]. In 2008 and 2012, three large multicenter investigator-initiated RCTs were published that demonstrated increased renal failure associated with HES 200/0.5 or HES 130/0.4 in critically ill and septic patients [14, 40, 43].

In 2013, a Cochrane Collaboration systematic review examined the effects of HES on kidney function compared to other fluid resuscitation therapies in different patient populations. The review included 42 studies (11,399 patients). Overall, there was a significant increase in the need for RRT in the HES-treated individuals compared to individuals treated with other fluid therapies (RR, 1.31, 95% CI, 1.16–1.49; 19 studies, 9857 patients) and the number with author-defined kidney failure (RR, 1.59, 95% CI, 1.26–2.00; 15 studies, 1361 patients). The RR of acute kidney injury (AKI) based on RIFLE-F (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease—Failure) criteria also showed an increased risk of AKI in individuals treated with HES products (RR, 1.14, 95% CI, 1.01–1.30; 15 studies, 8402 participants). No differences between subgroups for the RRT and RIFLE-F based outcomes were seen between sepsis versus nonsepsis patients, high Mw and DS versus low Mw and DS (≥200 kDa and >0.4 DS vs. 130 kDa and 0.4 DS) HES solutions, or high- versus low-dose treatments (i.e., ≥2 l vs. <2 l). The authors concluded that the current evidence suggests that all HES products increase the risk in AKI and RRT in all patient populations and a safe volume of any HES solution has yet to be determined [79]. A Canadian group evaluated the association of HES use with mortality and acute kidney injury in acutely ill patients from 28 HES solution trials. Starches, regardless of degree of molar substitution or molecular weight, were associated with increased use of renal replacement therapy among 9258 patients (RR, 1.32; 95% CI, 1.15–1.50) [57].

Kidney Failure in Surgical or Trauma Patients

The question whether HES administration in these patient populations impairs organ function cannot be definitively answered for lack of large randomized controlled trials with an adequate follow-up, but there is some strong suggestion that HES may also impair kidney function in these patients. Recently, the FLASH trial with abdominal surgical patients found that the pre-specified seondary endpoint AKI occurred significantly more often in the HES group (23%) than the saline group (17%, relative risk 1.36 (1.02–1.82, p = 0.04) [54]. To date, the results if this trial have not yet been included in meta-analyses. Feldheiser et al. performed a double-blind RCT with a 90-day follow-up in 50 patients undergoing gynecological cancer who received either HES 130/0.4 or crystalloid; however, not surprisingly given the small sample size, they found no difference in creatinine levels during the hospital stay [59]. James et al. randomized a total of 115 patients with blunt or perforated traumatic injuries to either HES 130/0.4 or crystalloids; 2/56 (3.6%) patients in the HES group and 3/53 patients in the crystalloid group (5.7%) received RRT; this effect was not significant given the small study sample [41]. Yates et al. assigned 202 medium- to high-risk patients undergoing colorectal surgery to receive either chloride-poor 6% HES 130/0.4 or Hartmann's. The number of patients with any predefined complications was 46% in the HES and 38% in the crystalloid group; among the complications, renal failure occurred in 4/104 in the HES versus 0/98 patients in the crystalloid group [64].

Several observational trials, which used statistical methods of adjustment, reported dose-dependent impact of HES administration on renal function. Rioux et al. retrospectively evaluated the risk of acute kidney injury by consensus criteria using pentastarch 10% (250 kDa, 0.45) in a random cohort of 563 cardiac surgical patients. Fifty-four (10%) patients developed AKI; pentastarch remained independently predictive of AKI, with an adjusted odds ratio per ml/kg of 1.08 (95% CI 1.04–1.12, $p = 0.001$). This risk was dose-dependent, and the optimal cutoff volume predicting AKI was 14 ml/kg [80]. Kashy et al. evaluated the data of adults without preexisting kidney failure who had inpatient noncardiac surgery from 2005 to 2012. Among a total of 29,360 patients and after controlling for potential confounding variables, the odds of developing a more serious level of AKI with Hextend (HES 450/0.7) was 21% (6–38%) greater than with crystalloid only ($P = 0.001$) and increased as a function of colloid volume ($P < 0.001$) [81]. Bayer et al. analyzed a prospective observational cohort of 6478 consecutive patients with cardiopulmonary bypass surgery and found that renal replacement therapy was more common during periods when patients received synthetic colloids compared to only crystalloids. Risk of renal replacement therapy was greater after HES (mostly HES 130/0.4, odds ratio, 2.29; 95% CI 1.47–3.60) and gelatin (odds ratio, 2.75; 95% CI, 1.84–4.16; both $p < 0.001$) compared to crystalloid. Propensity score stratification confirmed greater use of RRT in the HES and gelatin periods compared to the crystalloid period (odds ratio, 1.46 [1.08, 1.97]; $p = 0.013$ and odds ratio, 1.72 [1.33, 2.24]; $p < 0.001$, respectively) [47]. Opperer et al. retrospectively assessed data from 510 different hospitals across the United States with 1,051,441 patients undergoing

elective total hip and knee arthroplasty and compared outcomes in patients who never received any colloid with those who received 6% HES or 5% albumin. Perioperative fluid resuscitation with HES was associated with an increased risk of acute renal failure (adjusted odds ratio 1.23 [95% CI 1.13–1.34]), cardiac complications (OR 1.22 [1.13–1.31]), pulmonary complications (OR 1.22 [1.11–1.33]), and intensive care unit admission (OR 1.53 [1.45–1.60]) [82].

A current and extensive meta-analysis compared the effect of HES with non-HES control fluid in adult surgical patients on renal replacement therapy (RRT) including 15 randomized trials with a total of 4409 surgical patients. HES significantly increased recourse to RRT, with a pooled relative risk of 1.44 and 95% CI of 1.04–2.01. The absolute risk increase of recourse to RRT attributable to HES was 1.2% (95% CI: 0.1–2.2%), indicating a number needed to treat with HES of 85 to prompt RRT in 1 additional patient. In a subset of trials comparing HES 130/0.4 with crystalloid, the pooled RR for recourse to RRT (1.47; 95% CI: 1.02–2.12) coincided closely with the overall pooled RR of 1.44 [83].

On the other hand, some selective meta-analyses that were funded or initiated by HES manufacturers have come to the conclusion that HES administration in surgery has no side effects. Jacob et al. published a meta-analysis on side effects of HES in cardiac surgery, which was commissioned by an HES manufacturer, and concluded that no safety issues could be identified in terms of blood loss, transfusion requirements, or hospital length of stay [84]. However, a number of methodological concerns have been pointed out in critical letters [85, 86]: lack of assessment of bias, which was identifiable in 65% of included trials; severe confounders that should have led to exclusion of included trials, for instance, because of considerable use of HES in the control arms in seven trials or concomitant use of albumin in the HES group in six trials that may have mitigated the effects; use of false data thereby inflating the blood loss difference in one trial by 2.3-fold; omission of data from four trials that all showed increased bleeding attributable to HES; omission of data from an unpublished trial that showed high blood loss in the tetrastarch group, which had been included in previous meta-analyses; and aggregation of intra- with postoperative blood loss and preferential use of calculated rather than measured blood loss, which all confounded the estimation [85, 86]. Another severely flawed meta-analysis was published by van der Linden et al., which concluded that HES 130/0.4 was safe in surgery [87]. This analysis was funded by an HES manufacturer and conducted by a public relations firm. It ignored unfavorable data from several randomized controlled trials but included study data from two trials that had an unlabeled artificial oxygen carrier solution as control, as was pointed by Takala et al. [88].

Liver Dysfunction and Hydroxyethyl Starch Storage Disease

Storage of HES after infusion was reported in liver [19]; repeated infusions in patients with chronic liver disease led to worsening of liver function and diffuse microvacuolization of Kupffer cells in liver biopsies [89]. In the CHEST trial, which randomized 7000 ICU patients to either HES 130/0.4 or saline, patients in the HES

group had an increased risk of new hepatic dysfunction, reported as increased risk for hepatic SOFA subscore (RR 1.56; 95% CI 1.03–2.36, $p = 0.03$) [14]. HES was also detected in placenta [28], in lung, kidney, and spleen with altered organ morphology [26], and in the kidney after as long as 6 years [34]. HES may also affect the brain; a follow-up of patients from a randomized controlled sepsis trial who received HES revealed worse scores on the mental health portion of the quality-of-life questionnaire than patients who had received crystalloids [90]. Repeated HES administration, for instance, during plasmapheresis, may lead to an acquired lysosomal storage disease [91] and storage of HES in bone marrow and liver may result in persistent thrombocytopenia and liver dysfunction [92].

Pruritus can develop as a result from HES storage. The dermatologist Stander et al. identified the origin of HES-related itching as a deposit of the molecule in skin nerves [31]. A retrospective study by her group found that the median latency between HES exposure and pruritus onset was 3 weeks, and the median duration of pruritus was 6 months. Pruritus was severe, or very severe, in 80% of patients. Although the median cumulative dose of HES was 300 g, 15% of patients developed pruritus after only 30 g. The authors could find no significant differences between HES 130/0.4 and HES 200/0.5 in pruritus latency, duration, or severity and concluded that HES-induced pruritus may occur at any dose, molecular weight, or substitution [30]. In the CHEST trial with 7000 ICU patients, pruritus occurred in 4% of patients in the HES group and in 2.2% of patients in the crystalloid group [14].

Quality of Life After Sepsis

Wittbrodt et al. performed a post hoc analysis of Danish survivors ($n = 295$) from a large-scale, double-blinded randomized controlled trial that compared tetrastarch with crystalloids for fluid resuscitation in sepsis. Median 14 months (interquartile range 10–18) after randomization, 182 (61%) and 185 (62%) completed questionnaires were obtained. Patients in the HES group scored worse in bodily pain and 49% of patients allocated to HES had experienced pruritus at any time after ICU discharge compared to 43% of those allocated to Ringer's (RR 1.13, 95% CI 0.83–1.55, $P = 0.43$) [90].

Pediatric Patients

Clinical studies in pediatric patients are small and inconclusive. However, a very recent meta-analysis of RCTs involved pediatric patients who received 6% low-molecular-weight (130 and 200 kDa) HES and finally included a total of 13 RCTs involving 1156 patients [93]. Trial quality was overall low. In comparison to other fluids, HES did not significantly decrease the mortality (RR = −0.01; 95% CI: −0.05 to 0.03; $P = 0.54$) and blood loss (mean difference [82] = 17.72; 95% CI: −41.27 to 5.82; $P = 0.10$). There was a trend toward increased creatinine levels in the HES group (MD = 1.81; 95% CI: −0.35 to 3.98; $P = 0.10$). HES significantly decreased the blood

platelet count (MD = 20.99; 95% CI: −32.08 to −9.90; $P = 0.0002$) and increased the length of ICU stay (MD = 0.94; 95% CI: 0.18–1.70; $P = 0.02$). The authors concluded that volume expansion with 6% HES significantly decreased the platelet count and increased the length of ICU stay, and might have an adverse effect on renal function [93]. In the absence of manifest clinical benefit, and given the documented risks, administration of HES in pediatric patients seems not to be indicated.

The Dilemma

The December 2013 European Union (EU) regulation created a dilemma which the recent decision in July 2018 has not solved. In member countries such as the United Kingdom and Italy, national medical authorities had removed the product based on concerns for patient safety, but must now, according to regulations, reintroduce HES against the recommendation of their national societies. In addition, the EMA requested two post-marketing studies in perioperative and trauma patients with which it may prove difficult to comply. Clinicians who believe—as did a considerable proportion of the EMA review board (Box 12.2) [2]—that the safety of HES is not reliably established in the patients, may not want to administer HES and patients who are fully informed might not want to receive a drug proven harmful in some settings with no reason to suggest a different effect in elective surgery or trauma patients. The available studies in these populations provide no assurance of a lower risk of mortality and kidney failure than in critically ill patients, nor were there any new studies in such patients to justify the revised decision. Moreover, the recent FLASH trial in abdominal surgery - the largest RCT to date with over 700 patients - confirms previous concerns by demonstrating a lack of benefit for the patient but additional harm including increased blood loss, more AKI and a trend towards higher mortality after HES [54]. Thus, treating acute blood loss in surgical and trauma patients with a substance that increases coagulopathy and is also otherwise harmful seems paradoxical. Lastly, lack of relevant benefit in trauma patients—and a nominally 10% higher mortality rate—was demonstrated in the first RCT [42] and in one retrospective study [94]. In the perioperative setting, the only RCT assessing a 90-day survival endpoint found a higher mortality rate using HES (0 vs. 5 patients died, $p = 0.051$) [59]. Moreover, no safe dose for HES has been defined [79]. Kidney failure occurred in intensive care patients after a mean dose of 7.5 ml/kg/day, a fraction of the maximal dose of 30 ml/kg of HES that is now applicable according to current legislation [14].

Conclusion

Without evidence to provide reassurance that patients will not be exposed to increased risk of mortality and renal injury by use of HES, and given the lack of data supporting a clinically relevant benefit, suspension of marketing authorizations for HES products in all patient populations remains appropriate to protect public health. Use of HES in surgical or trauma patients is not formally restricted according to the

2013 and 2018 European Commission majority decision, but this decision is questionable. HES side effects regarding bleeding impairment and kidney failure have been reported in all patient populations and significant risks are detected in well-performed meta-analyses also in surgical populations. HES is more expensive than crystalloids and high-quality care is possible without its use. There is no compelling reason to use it in surgical or trauma patients.

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