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Review

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Understanding the Harms of HES: A Review of the Evidence to Date

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Abstract

Intravenous (IV) fluid resuscitation is one of the most common interventions in intensive care medicine. Despite clear guidelines, the choice of IV fluid is largely dependent on physician preference instead of high-quality evidence of efficacy and safety. This is particularly the case for synthetic colloids, such as hydroxyethyl starch (HES). The use of HES in critical care has been associated with increased rates of acute kidney injury (AKI), renal replacement therapy and mortality. In light of this, current guidelines and scientific and regulatory bodies do not recommend the use of HES for fluid therapy in critical illness and caution against its use in many other settings. Despite this, HES products are still debated and used. Awareness of the indications, contraindications, doses, benefits and adverse effects for IV fluids, as well as recommendations from scientific and regulatory bodies, is essential to guarantee patients' safety. Poor awareness of optimal IV fluid therapy has recently been revealed in some countries including Turkey. Therefore, we provide a review of fluids used for resuscitation, discuss safety data and adverse effects of HES, such as increased AKI and mortality, and discuss recent updates from scientific and regulatory bodies in order to raise awareness of fluid therapy. We conclude that given the lack of a clear benefit of HES in any clinical setting and the availability of safer alternatives, such as crystalloids and albumin, HES should be avoided.

Keywords: Acute kidney injury, AKI, critical illness, crystalloids, colloids, fluids, HES, hydroxyethyl starch, mortality, resuscitation, sepsis

Introduction

Intravenous (IV) fluid resuscitation is a medical intervention primarily aimed at restoring intravascular volume and maintaining tissue perfusion following the loss of circulating blood volume due to sepsis, extensive burns or severe bleeding (e.g. trauma and surgery), among other medical causes. Resuscitation fluids are generally categorised into crystalloids and colloids. Crystalloids are solutions of water and ions (e.g. sodium and chloride) permeable to the capillary membrane. The most commonly used crystalloids are normal saline (non-balanced, 0.9% sodium chloride solution) and Ringer's lactate (balanced, buffered with sodium lactate solution). Colloids are water-based solutions with both permeable small ions and non-permeable molecules. Colloids may be natural, such as albumin, or synthetic, such as hydroxyethyl starch (HES), gelatin and dextran. The selection of resuscitation fluid is highly dependent on physician preference, with great regional variability. Instead, IV resuscitation fluids should be treated as any other IV drug, and thus the choice and administration of IV fluids should be informed by high-quality evidence of efficacy and safety, particularly since fluid therapy is one of the most common interventions in intensive care medicine. Specific treatment guidelines, such as the 'Surviving Sepsis Campaign International Guidelines for Management of Severe Sepsis and Septic Shock' (1), recommend crystalloids as first-line therapy for resuscitation of patients with sepsis and septic shock. The use of albumin in addition to crystalloids is suggested when patients require substantial amounts of crystalloids to maintain intravascular volume; however, the guidelines recommend against the use of HES for fluid resuscitation in severe sepsis and septic shock due to its adverse effects, such as increased risk of acute kidney injury (AKI), renal replacement therapy (RRT) and mortality (Figure 1) (2-4).

A recent epidemiological study of sepsis in Turkish intensive care units (ICUs) reported excessively high mortality rates from sepsis and septic shock (55.7% and 70.4%, respectively) (5). A previous multicentre survey reported that

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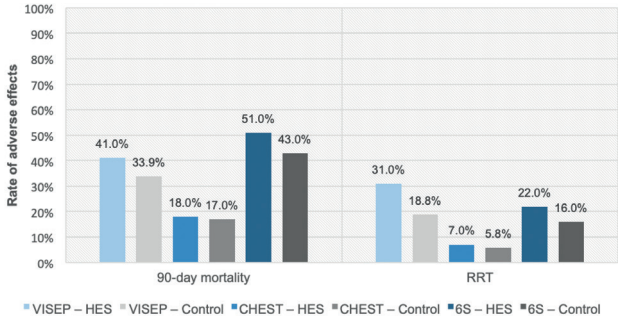

Figure 1. Adverse effects of HES reported in RCTs
Rate of 90-day mortality and renal replacement therapy (RRT) in patients treated with hydroxyethyl starch (HES) (blue) compared with a control fluid (grey) for VISEP, CHEST and 6S randomised clinical trials (RCTs)

only 40% of physicians in charge of patients with sepsis in Turkey were aware of fluid resuscitation and had poor knowledge of the Surviving Sepsis Campaign bundles (6). Therefore, the high rate of mortality in patients with severe sepsis in Turkish ICUs may be due to delayed treatment and poor compliance with sepsis guidelines. Awareness and adherence to the Surviving Sepsis Campaign bundles is key to reducing sepsis-related mortality. Therefore, physicians in Turkish centres should be trained in sepsis management guidelines and the use of IV fluids.

Similarly to the Surviving Sepsis Campaign International guidelines and EU and US regulatory bodies (7-9), the Turkish regulatory bodies and associations (10) discourage the use of HES in patients with sepsis, severe sepsis and septic shock and critical illness; intensive care patients and patients undergoing open heart surgery or cardiopulmonary bypass due to the risk of bleeding, as well as in patients with acute severe liver failure or those with a history of renal dysfunction (see Table 1 for a summary of recommendations on colloids in Turkey). Additionally, they advise that for patients with chronic liver disease, a risk-to-benefit assessment should be performed, and patients should be kept under observation. Furthermore, it is recommended that HES should be terminated at the first sign of kidney injury or discontinued at the first sign of coagulopathy, and that in all patients, renal function should be continuously assessed for at least 90 days. Despite these contraindications and limitations, there is global evidence that HES continues to be used in these situations (9, 11, 12).

In light of the recurrent use of HES and poor awareness of optimal fluid replacement therapy in Turkey, the aims of this review were to examine the evidence on the use of HES in fluid resuscitation, to discuss safety data and adverse effects, such as increased AKI and mortality, and to place these data in context with recent guidelines and updates from scientific and regulatory bodies.

Clinical evidence of HES adverse effects

In 1972, the first HES solution (Hespan, 6% HES 600/0.7) was approved by the US Food and Drug Administration (FDA). Approval was based upon data from non-controlled studies with a small sample size (315 patients) and short observation period (<24 h) (13, 14). However, soon after, there were repeated reports of HES interfering with coagulation, leading to increased bleeding (15-17). Evidence of other adverse effects started to emerge (i.e. pruritus and impaired renal function), and tissue accumulation of HES was observed in humans and animals (18-22). Despite the early documentation of the adverse effects of HES, it was not until 2001 that a randomised controlled trial (RCT) demonstrated an increased risk of AKI in patients with sepsis treated with HES compared with gelatin (23). Schortgen et al. (23) assessed the effect of HES on renal function in severe sepsis and demonstrated that HES is associated with an increased risk of AKI in these patients (odds ratio (OR) 2.57, 95% confidence interval (CI) 1.13–5.83). Following this evidence, an FDA hearing sought to determine the effects of Hespan (6% HES in 0.9% saline) and Hextend (6% HES in lactated electrolyte solution) on coagulation and blood loss; the regulators issued a boxed warning for Hespan but not Hextend (24). Thereafter, in 2007, a modified HES with lower molecular weight (Voluven, 6% HES 130/0.4) and alleged fewer adverse effects (25) was approved by the FDA. Only a few years later, large RCTs reported increased risks of AKI, RRT and mortality in patients with sepsis and ICU patients treated with HES compared with crystalloids (2-4). Based on this evidence, in 2013, the FDA issued a boxed warning for all HES products regarding the risk of renal injury and mortality in critically ill patients (7), and the European Medicines Agency (EMA) recommended not to use HES in patients with sepsis or burn injuries or in those critically ill (8).

Use of HES solutions in critical illness

In 2008, Brunkhorst et al. (2) published a large RCT on the adverse effects of HES. The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial compared the use of HES 200/0.5 with Ringer's lactate for fluid resuscitation in 600 patients with severe sepsis. Compared with Ringer's lactate, HES was associated with significantly higher rates of 90-day mortality (41% (95% CI 35.0–47.0) vs. 33.9% (95% CI 28.3–39.6), p=0.09), AKI (34.9% (95% CI 29.1–40.7) vs. 22.8% (95% CI 17.8–27.8), p=0.002) and RRT (31.0% (95% CI 25.4–47.0) vs. 18.8% (95% CI 14.1–23.4), p=0.001). In 2012, two further large RCTs reported similar results (Figure 1). The Crystalloid versus Hydroxyethyl Starch Trial (CHEST) evaluated the safety and efficacy of 6% HES 130/0.4 compared with 0.9% saline in 7000 ICU patients (3). While the 90-day mortality was not significantly different between the HES and saline groups (18.0% vs. 17.0%, relative risk (RR) 1.06, 95% CI 0.96–1.18, p=0.26), HES was

Table 1. Summary of recommendations on colloids in Turkey

Colloid	Indications*	Contraindications/restrictions†
Hydroxyethyl starch	Hypovolaemia	**Contraindicated in patients with:**
	Hypovolaemic shock	Sepsis
		Burns*
		Critical illness
		Severe coagulation disorder
		Severe heart failure
		Renal insufficiency
		Renal replacement therapy
		Oliguria and anuria
		Hyperhydration
		Intracranial or cerebral haemorrhage
		Known hypersensitivity to HES
		Severe hypernatraemia
		Severe hypochloraemia
		Fibrinogen deficiencies
		Severe haemorrhagic diathesis
		Pulmonary oedema
		Hypervolaemia
		Organ transplant patients
		Severe liver disease
		Cautious use in:
		Severe chronic liver disease
		Severe cases of von Willebrand's disease
		Pulmonary oedema
		Heart failure
		Renal failure/dysfunction
		Chronic liver disease
		Haemorrhagic diathesis
		Dehydration due to reduced extracellular volume
		Hypernatraemia or hypochloraemia
		Pregnancy, children and nursing mothers
		Surgery and trauma patients*
		Patients receiving dialysis
		Critically ill patients
		Monitor:
		Serum creatinine
		Electrolyte levels and fluid balance
		Renal function for at least 90 days
Albumin	Intensive care/patients with sepsis not responding to crystalloids	Hypersensitivity to albumin Cautious use in patients with haemodilution with hypervolaemia
Gelatin	Hypovolaemia Shock Acute normovolaemic haemodilution	Hypervolaemia Hyperhydration Hypersensitivity to sodium hydroxide or hydrochloric acid **Cautious use in patients with:** Renal insufficiency Asthma

Table 1. Summary of recommendations on colloids in Turkey (continued)

Colloid	Indications*	Contraindications/restrictions†
Hydroxyethyl starch	Hypovolaemia	**Contradicted in patients with:** Pulmonary oedema with hypertension Cardiac insufficiency Severe renal dysfunction Water/salt retention Severe coagulation disorder **Monitor:** Haemodynamic, haematological and coagulation systems Haematocrit and electrolytes Plasma protein concentration

*Burns, trauma and surgery listed as indications by BioHES 6%, IsoHES 6% and VariHES 6%.
†Contradictions/restrictions and cautions for HES use were all different among brands.

Table 2. Methodological limitations of RCTs reporting the safety of HES products in critical illness

RCT	Setting	No. of patients	Methodological limitations
FIRST (26)	Trauma	115	• Missing data, including site of injury, pre-study crystalloid volume, baseline SOFA score, time to resuscitation targets and mortality by group • Downplayed data, increase in transfusion of blood products in HES versus saline in blunt trauma • Lack of statistical power due to small sample size • Flawed randomisation • Poor matching at baseline of the study groups • Statistical analysis inadequately described or incompletely performed • Discrepancies between pre-specified and reported endpoints
CRYSTMAS (27)	Severe sepsis	196	• Lack of statistical power due to small sample size • Renal safety data incompletely reported • Missing data • Trial outcomes selectively published • Discrepancies between pre-specified study protocol and publication
CRISTAL (28)	ICU-hypovolaemic shock	2857	• Lack of allocation concealment and blinding • Baseline imbalance between the study groups 12 h prior to randomisation • Variety of fluids used in the two groups with lack of stratification within groups

HES: hydroxyethyl starch; ICU: intensive care unit; RCT: randomised clinical trial; SOFA: Sequential Organ Failure Assessment

associated with a significant increase in the use of RRT (7.0% vs. 5.8%, RR 1.21, 95% CI 1.00–1.45, p=0.04) and a higher rate of treatment-related adverse events, such as pruritus and skin rash (4.6% vs. 3.3%, p=0.006). The Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial studied the safety of HES 130/0.4 compared with Ringer's acetate in 804 patients with severe sepsis (4). The results demonstrated that HES, compared with Ringer's acetate, was associated with significantly increased 90-day mortality (51% vs. 43%, RR 1.17, 95% CI 1.01–1.36, p=0.03) and use of RRT (22% vs. 16%, RR 1.35, 95% CI 1.01–1.80, p=0.04).

Around the same time, three other RCTs reporting no adverse effects of HES were published (26-28); however, these studies suffered from serious methodological limitations (Table 2). The Fluids in Resuscitation of Severe Trauma (FIRST) trial investigated the safety and efficacy of HES 130/0.4 compared with 0.9% saline in 115 patients with blunt or penetrating trauma (26).

The study reported no differences in renal injury in blunt trauma between resuscitation fluids (20% vs. 14% for HES and saline, respectively) and a significantly reduced incidence of renal injury in penetrating trauma patients treated with HES compared with saline (0% vs. 16%, p=0.018). However, the FIRST study was strongly criticised for several major flaws, such as downplaying the increase in transfusion of blood products in blunt trauma patients treated with HES compared with saline (mean transfusion of packed red blood cell (RBC) volumes: 2943 (1628) vs. 1473 (1071) mL, p=0.005), lack of statistical power to accurately assess the differences in renal function due to the small sample size, missing key data, flawed randomisation and poor matching at baseline of the study groups, incomplete or inadequately described statistical analyses and discrepancies between pre-specified and reported endpoints (29, 30). Additionally, James et al. (26) only reported data on mortality in a letter to the editor after Finfer (30) raised the question of the missing data from the FIRST study. The CRYSTalloids Morbidity Associated with severe Sepsis (CRYSTMAS) trial investigated the efficacy and safety of HES 130/0.4 compared with 0.9% saline in 196 ICU patients with severe sepsis (27). The study reported no differences between the HES and saline groups in AKI (24.5% vs. 20%, p=0.454), 28-day mortality (31% vs. 25.3%, p=0.37) and 90-day mortality (40% vs. 34%, p=0.33). However, the study was underpowered to assess AKI and mortality and was criticised for incompletely reporting renal safety data, failing to report key data and selectively publishing trial outcomes (31, 32). The Therapy in the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial assessed the effects of colloids (HES, gelatin, dextran and 4% or 20% albumin) and crystalloids (Ringer's lactate and isotonic or hypertonic saline) on mortality in 2857 ICU patients with hypovolaemic shock (28). The study reported no significant difference in 28-day mortality between resuscitation fluids (25.4% vs. 27% for colloids and crystalloids, respectively, RR 0.96, 95% CI 0.88–1.04, p=0.26) and need for RRT within the first 28 days (11.3% vs. 11.4% for colloids and crystalloids, respectively, RR 0.8, 95% CI −1.6–3.3, p=0.90); 90-day mortality was higher in the crystalloids group than in the colloids group (34.2% vs. 30.7% for crystalloids and colloids, respectively, RR 0.92, 95% CI 0.86–0.99), p=0.03). However, the study had several methodological issues, including lack of allocation concealment and blinding which may have led to an overestimation of the intervention effects, baseline imbalance between the study groups 12 h prior to randomisation and a mixture of fluids in the study groups with lack of stratification within the two groups of fluids (33, 34). A recent observational study (RaFTinG) assessed the relationship between IV fluid therapy (crystalloids and colloids) and 90-day mortality, ICU mortality, AKI and RRT in ICU patients (35). After full multivariate adjustment, the study reported no significant negative effects of 6% HES 130/0.4 on 90-day mortality (hazard ratio 0.833, 95% CI 0.656–1.057), ICU mortality (OR 0.700, 95% CI 0.637–0.769), AKI (OR 0.800, 95% CI 0.704–0.910) or RRT (OR 0.509, 95% CI 0.441–0.586). However, these results contrasted strongly with the unadjusted and baseline-adjusted results, which clearly demonstrated significantly higher risk of these outcomes in patients treated with HES. This may have been a consequence of over-adjustment, which the authors acknowledged, advising that the fully adjusted results be interpreted with caution.

RCTs reporting the adverse effects of HES are further supported by systematic reviews and meta-analyses (36-42). One of the largest meta-analyses to date included 42 RCTs, with a total of 11,399 patients, including those with sepsis or burns (8 studies, 3899 patients) and non-septic surgical and trauma patients (11 studies, 5911 patients) (36). Mutter et al. (36) assessed the safety of HES products (6% HES 130/0.4, 200/0.5, 200/0.6 or 450/0.7) compared with different resuscitation fluids (crystalloids, albumin, gelatin and blood or fresh frozen plasma (FFP)). Their analysis revealed significant increases in the need for RRT (19 studies, 9857 patients, RR 1.31, 95% CI 1.16–1.49), risk of AKI based on RIFLE-F (failure) (15 studies, 8402 patients, RR 1.14, 95% CI 1.01–1.30) and author-defined kidney failure (15 studies, 1361 patients, RR 1.59, 95% CI 1.26–2.00) in patients treated with HES compared with other fluids. No significant differences in these outcomes were observed between patients with sepsis and without sepsis. Additionally, the significantly higher risk for RRT in patients treated with HES compared with other fluids was independent of HES molecular weight (high-molecular weight: 9 studies, 1183 patients, RR 1.56, 95% CI 1.15–2.11 and low-molecular weight: 10 studies, 8353 patients, RR 1.26, 95% CI 1.09–1.45) and volume of HES infused (high volume (≥2 L): 10 studies, 2220 patients, RR 1.43, 95% CI 1.20–1.71 and low volume (<2 L): 7 studies, 7296 patients, RR 1.22, 95% CI 1.02–1.46). Zarychanski et al. (37) presented similar results when assessing the effects of HES administration on AKI and mortality. HES administration was associated with increased mortality (10,290 patients, RR 1.09, 95% CI 1.02–1.17), renal failure (8725 patients, RR 1.27, 95% CI 1.09–1.47) and need for RRT (9258 patients, RR 1.32, 95% CI 1.15–1.50). Haase et al. (38) also demonstrated a higher risk of RRT in patients with sepsis treated with HES 130/0.38–0.45 compared with other resuscitation fluids (5 studies, 1311 patients, RR 1.36, 95% CI 1.08–1.72). Similarly, Patel et al. (40) reported increased 90-day mortality (6 studies, 3033 patients, RR 1.13, 95% CI 1.02–1.25) and need for RRT (6 studies, 3033 patients, RR 1.41, 95% CI 1.08–1.84) in patients with sepsis treated with HES 6% 130/0.4 and 130/0.42 compared with crystalloids. Serpa-Neto et al. (41) examined the effects of fluid resuscitation with HES solutions (10% HES 200/0.5 or 6% HES 130/0.4) compared with other fluids in patients with sepsis (10 studies, 4624 patients). The results revealed significantly higher risks of AKI (RR 1.24, 95% CI 1.13–1.36), need for RRT (RR 1.36, 95% CI 1.17–

1.57) and 90-day mortality (RR 1.14, 95% CI 1.04–1.26) in patients treated with HES. In line with the findings of Mutter et al. (36), the adverse effects of HES reported by Serpa-Neto et al. (41) were independent of HES molecular weight. In a network meta-analysis, Rochwerg et al. (42) investigated the association of different resuscitation fluids (low- and high-molecular weight HES, crystalloids, albumin and gelatin) with need for RRT in patients with sepsis. The study reported a higher risk for RRT in patients treated with HES compared with crystalloids (OR 1.39, 95% credibility interval 1.17–1.66). Significantly higher risks of mortality, AKI and RRT in patients resuscitated with HES compared with other fluids have been demonstrated in both patients with sepsis and without sepsis (36, 37, 39). For instance, Gattas et al. (39) reported increased risks of RRT (11 studies, 8496 patients, RR 1.25, 95% CI 1.08–1.44) and mortality (25 studies, 9411 patients, RR 1.08, 95% CI 1.00–1.17) in acutely ill patients, including both patients with sepsis and without sepsis, resuscitated with 6% HES 130/0.4 and 130/0.42.

The evidence that HES solutions are associated with adverse effects, such as AKI, RRT and mortality, in intensive care and critically ill patients is overwhelming, and consequently, their use in these patients is prohibited. Indeed, based on the extensive evidence available, regulatory bodies and treatment guidelines endorse the banning of HES products in sepsis, intensive care and critically ill patients.

Use of HES solutions in surgery

In 2013, three Turkish studies assessed the effects of fluid resuscitation with HES in cardiac surgery patients and concluded that HES had no adverse effects on renal function (43-45). Durukan et al. (43) compared 6% HES 130/0.4 with a balanced electrolyte solution in 157 patients undergoing coronary artery bypass surgery. The study reported no differences between fluids in postoperative exploration for haemorrhage (2.5% vs. 1.3% for HES and crystalloid, respectively, OR 2.0, 95% CI 1.1–119.5, p=1.000), mean amount of blood and blood products transfused (FFP, RBC and platelet concentrate, all p>0.1) and postoperative renal dysfunction (6.3% vs. 3.8% for HES and crystalloid, respectively, OR 1.7, 95% CI 0.3–11.2, p=0.719). Akkucuk et al. (45) assessed the effects of 6% HES 130/0.4 and Ringer's lactate on renal function in 24 paediatric patients undergoing cardiac surgery. The study reported no evidence of first-stage AKI in either fluid group, measured as an increase in serum creatinine levels. Gurbuz et al. (44) studied the effects of 6% HES 130/0.4 compared with a balanced electrolyte solution in 200 patients undergoing coronary bypass surgery. The results found no increased postoperative exploration for haemorrhage (5% vs. 2% for HES and crystalloid, respectively, p=0.445), mean blood and FFP used (both p>0.1) and renal dysfunction (9% vs. 6% for HES and crystalloid, respectively, p=0.421). These three studies are severely limited by the use of serum creatinine as a surrogate indicator of renal injury, which has been shown to lack sensitivity and predictive value as a marker of underlying renal injury. Moreover, the studies by Durukan et al. (43) and Akkucuk et al. (45) are limited by the low number of patients included (<200 patients) (46). Similar issues undermined a 2018 study by Kammerer et al. (47) who compared HES 6% 130/0.4 with albumin 5% in 100 patients undergoing elective cystectomy. The study concluded that HES 6% 130/0.4 and albumin 5% had comparable safety profiles in non-critically ill patients undergoing major surgery. However, this trial was probably underpowered given that the actual standard deviation of cystatin C values at baseline (approximately 0.36 mg dL^{-1}) (48) was larger than that originally used for sample size calculation (0.2 mg dL^{-1}) (49). A larger sample size would almost certainly be required to ensure a power of 80% to detect clinically meaningful differences between the two groups. Moreover, patients with reduced glomerular filtration rates were excluded; the selection of patients with the lowest possible risk of renal injury is not reflective of real-world practice and represents an inherent bias. In addition, Kammerer et al.'s chosen marker of renal injury, cystatin C, is not validated for the detection of AKI. A more reliable and validated marker, such as neutrophil gelatinase-associated lipocalin, may have been more appropriate as the primary endpoint (50). The study also imputed missing data points for cystatin C at day 90 (primary endpoint), replacing these with a value greater than the observed cystatin C ratios to ensure a pessimistic/conservative approach. However, this disadvantaged the albumin group, which had more missing data and which also appeared sicker at the start of the study (trend towards higher American Society of Anesthesiologists score).

The use of HES in elective surgery patients is not supported by high-quality evidence of its safety in perioperative settings. On the contrary, the lack of large high-quality RCTs with long-term follow-up and large systematic reviews and meta-analyses precludes any conclusions regarding the safety of HES in surgical patients (51-54). Advocates for the use of HES in the operating room claim that findings from critically ill patients cannot be extrapolated to surgical patients (55), and that the adverse effects observed were due to the administration of HES after the initial stabilisation phase (56-59). Despite the lack of evidence, these authors support the use of HES for initial haemodynamic resuscitation (within <6 h from onset of shock) during surgery (55, 59, 60). Importantly, Navickis et al. (61) performed a meta-analysis of 18 RCTs comparing HES with albumin in 970 patients undergoing cardiopulmonary bypass surgery. The study reported significantly increased postoperative blood loss (33.3% increase of pooled SD, 95% CI 18.2%–48.3%), reoperation for bleeding (RR 2.24, 95% CI 1.14–4.40) and transfusion of blood and blood products (RBC: 28.4% increase of pooled SD, 95%

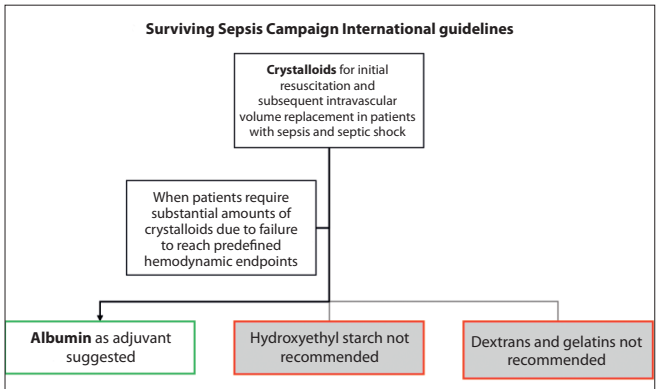

Figure 2. Flowchart of the Surviving Sepsis Campaign International guidelines

CI 12.2%–44.6%; FFP: 30.6% increase, 95% CI 8%–53.1% and platelets: 29.8% increase, 95% CI 3.4%–56.2%) in patients treated with HES. In a further meta-analysis, Wilkes and Navickis (62) analysed 15 RCTs with a total of 4409 surgery patients and reported a significantly increased need for RRT in patients treated with HES compared with other fluids (pooled RR 1.44, 95% CI 1.04–2.01). In a retrospective study, Kashy et al. (63) assessed the relationship between fluid therapy with HES versus non-colloids and the risk of AKI in 29,360 non-cardiac surgery patients. A significantly higher risk of developing AKI was observed with HES compared with crystalloids (adjusted OR 1.21, 97.5% CI 1.06–1.38). Similarly, Lagny et al. (64) demonstrated higher incidence of postoperative AKI in 606 patients undergoing cardiac surgery treated with 6% HES 130/0.4 compared with crystalloids (adjusted OR 2.26, 95% CI 1.40–3.80). In contrast, a meta-analysis of 19 RCTs with a total of 1567 patients did not find differences in AKI (risk difference (RD) 0.02, 95% CI −0.02–0.06, p=0.34), need for RRT (RD −0.01, 95% CI −0.04–0.02, p=0.62) or hospital mortality (RD 0.00, 95% CI −0.02–0.02, p=0.91) in surgical patients treated with 6% HES compared with other fluids (65). A retrospective study of 1442 surgery patients by Ahn et al. (66) reported an increased incidence of AKI only in patients with decreased renal function (OR 7.6, 95% CI 1.5–58.1, p=0.0109). Even though these two last studies did not clearly demonstrate an increased incidence of AKI in all surgical patients, the authors cautioned against the use of HES in the operating room based on the lack of evidence of any benefit of HES and its demonstrated adverse effects in the critically ill, and because patients undergoing major surgery often develop AKI and require critical care (65, 66).

Adverse effects, such as AKI, apply to all HES products. These are attributed to coagulopathy, which increases the risk of bleeding and need for blood products, and tissue storage, particularly in the skin and kidney, causing pruritus and nephrotoxicity, respectively (22, 67-70). To date, there is no compelling evidence that HES offers any benefit during surgery, nor that the risk of adverse events is lower in critical illness.

Is there a place for HES? An update from scientific and regulatory bodies

In 2013, after CHEST, VISEP and 6S demonstrated that the use of HES was associated with an increased risk of mortality and renal failure, the FDA recommended against the use of HES in critically ill patients (7). Initially, the EMA Pharmacovigilance Risk Assessment Committee (PRAC) suspended marketing authorisation for all HES products (71). However, after this suspension was challenged by the marketing authorisation holders, a second committee restricted suspension to the treatment of sepsis, burn and critically ill patients and those with renal impairment or receiving RRT or with severe coagulopathy (8). The PRAC allowed the use of HES in patients with hypovolaemia due to acute bleeding when not responding to crystalloids, with HES use restricted to no more than 24 h (lowest effective dose for the shortest period to achieve haemodynamic goals) with continuous haemodynamic monitoring and extended monitoring of kidney function for 90 days (8). Furthermore, the PRAC requested post-marketing RCTs to assess the safety of HES in surgical and trauma patients (72). Similarly, the Surviving Sepsis Campaign International guidelines do not recommend the use of HES for fluid resuscitation in patients with sepsis (Figure 2) (1).

In 2017, concerns that despite these restrictions HES solutions were still being used, particularly in settings where evidence was based on poorly controlled data and low-quality studies (73), led to a petition to ban the use of HES products, which was supported by many medical experts (74, 75). In 2018, the PRAC reviewed the results from drug utilisation studies of HES solutions, clinical evidence to date of HES benefits and risks and feedback from experts. The PRAC recommended that due to the serious risks of HES in certain patient populations and evidence that the 2013 restrictions had not been sufficiently effective, all marketing authorisations for all HES products should be suspended (9). This decision was endorsed by the CMDh, a medicines regulatory body representing the EU Member States, Iceland, Liechtenstein and Norway (76). However, recently, this decision was questioned by some countries (e.g. Germany, Czech Republic, France and Spain), which led the European Commission to suspend its decision-making process and request that the EMA and CMDh re-evaluate the PRAC recommendation (77). As an outcome, the EMA confirmed its original recommendation to suspend HES; however, the CMDh changed its position and recommended HES products to remain on the market provided that additional control measures to protect patients are implemented (78). These measures include: a controlled access programme by companies whereby only accredited hospitals will be supplied with HES products (accreditation achieved via a training programme of relevant healthcare professionals on the safe

use of HES solutions for infusion), warnings on the packaging that HES products should not be used in patients with sepsis or kidney impairment or in critically ill patients and direct written contact with healthcare professionals to ensure their awareness of the conditions and contraindications for the use of HES (78). Renowned experts have recently called for support from the World Health Organization to protect patients by banning the use of HES solutions worldwide (79). Until HES products are completely withdrawn, their use in cases where haemorrhagic-dependent hypovolaemia does not respond to crystalloids is subject, according to PRAC recommendations, to restrictions of duration (<24 h) and dose (<30 mL kg^{-1}), as well as renal monitoring for at least 90 days after infusion. Fulfilling such obligations will be labour intensive and will significantly increase the time and cost associated with the use of a resuscitation fluid that has demonstrated no clear benefit over other fluids in any clinical setting.

Conclusion

IV fluid therapy is crucial for the care of critically ill patients and patients undergoing major surgery. Fluids should be considered as drugs, and as such, physicians should be knowledgeable of their indications, contraindications, doses and potential benefits and adverse effects. To improve the awareness of fluid resuscitation options for physicians at Turkish centres, the present review provides a summary of fluids used for resuscitation, the established harms of HES and recent updates from regulatory bodies.

There is no evidence of a clear benefit of HES over other fluids in any setting, but there is overwhelming, high-quality evidence of the harms of HES in critically ill patients. HES should also be avoided in the operating room. Despite robust data on the adverse effects of HES, contraindications and warnings, there is evidence to suggest that HES use has continued in banned settings. Increased awareness, training and education on the harms of HES are needed, particularly in hospitals where awareness of the Surviving Sepsis Campaign is low. Given the lack of evidence of the benefit of HES, the increased time/cost of implementing additional control measures and the availability of safer alternatives (crystalloids and albumin), HES should be avoided altogether.

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