Hydroxyethyl Starches in the Perioperative Period. A review on the efficacy and safety of starch solutions

I. Ghiselings (*) and S. Rex (***)

Summary: Several randomized controlled trials have raised alarming concerns about the safety of hydroxyethyl starches (HES) for the hemodynamic stabilization of critically ill patients. It has been repeatedly demonstrated that the use of HES in patients treated in an intensive care unit was associated with an increased occurrence of serious adverse events, including a higher incidence of renal injury or failure, a higher need for renal replacement therapy (RRT), and (in one study) increased mortality.

HES solutions are also widely used in the perioperative period, although high-level evidence on both the efficacy and safety of HES in patients undergoing surgery is sparse. It is unknown to which extent the concerning findings in critically ill patients can be extrapolated to the perioperative setting, where a variety of distinct patient populations is encountered. However, caution and an increased awareness for possible adverse effects of HES solutions in the perioperative setting are warranted.

In 2013, the European Medicines Agency (EMA) concluded that the benefits of HES solutions no longer outweigh their risks, and therefore recommended that the marketing authorizations for these medicines be suspended (1). Upon request of some of the marketing-authorization holders (MAH), the EMA re-analyzed its recommendation. After a thorough review of the available data, the Pharmacovigilance Risk Assessment Committee (PRAC) concluded, on November 11th, that the increased risk of mortality and RRT or renal failure associated with the use of hydroxyethyl starch containing medicinal products outweighs their limited clinical benefits in the approved indications, and in any patient population. In June 2013, the U.S. Food and Drug Administration also communicated a serious warning with respect to the use of HES (2).

The present (non-systematic) review summarizes the evidence upon which these remarkable recommendations are based. Moreover, current guidelines on the use of HES are quoted.

Keywords: hydroxyethyl starch; volume resuscitation; acute renal injury; bleeding; mortality.

INTRODUCTION

Particularly in Europe, colloid solutions continue to enjoy widespread usage for volume resuscitation, most often in conjugation with crystalloids (3). The type of available fluids for resuscitation varies widely, and the choice of a specific resuscitation fluid is still mainly driven by personal preferences and experience. Hydroxyethyl starches (HES) are particularly frequently used (3).

Recently, several large-scale randomized controlled trials (RCT) have raised serious concerns about the safety of HES for the hemodynamic stabilization of critically ill patients (4-6). It has been repeatedly demonstrated that the use of HES in patients treated in an intensive care unit was associated with an increased occurrence of serious adverse events, including a higher incidence of renal injury or failure, a higher need for renal replacement therapy (RRT), and increased mortality. These observations have driven both the European Medicines Agency and the U.S. Food and Drug Administration to communicate warnings on the increased risks of HES solutions.

Most commonly, colloids are used for the maintenance or augmentation of intravascular volume. Therefore, HES is also widely used in the perioperative setting. However, high-quality data on the safety and efficacy of HES solutions when administered to patients during surgery are sparse. It has to be considered that distinct underlying pathophysiological conditions (in particular the presence or absence of a capillary leak) might result in different efficacy and safety profiles of HES-solutions. This complicates the extrapolation of the alarming safety data from the critical care to the intraoperative setting. In addition, there is a wide variability of available HES solutions,
displaying significantly different pharmacokinetic and -dynamic properties. This impedes a thorough assessment of the effects of HES.

The present (non-systematic) review therefore gives a brief overview on various important pharmacokinetic properties and the available (and sometimes confusing) evidence on the efficacy and safety of HES solutions. The aim of this review is to support the clinician in the evidence-based choice of an appropriate resuscitation fluid.

**Pharmacokinetics of HES**

Three numbers are used to characterize HES solutions, e.g., 10% HES 200/0.5 or 6% HES 130/0.4. The first number indicates the concentration that determines the colloid-osmotic pressure/oncoticity of the solution, hereby contributing to the initial volume effect: 6% HES solutions are iso-oncotic in vivo (i.e., having a colloid-osmotic pressure comparable to plasma, and achieving a volume effect of 100%), whereas 10% solutions are hyperoncotic (i.e. exhibiting a supra-physiologic colloid-osmotic pressure, and hence achieving a volume-effect above 100% by attracting water from the interstitial space into the intravascular compartment).

The second number represents the mean molecular weight (MW) of the specific HES solution. When a colloid is infused into the circulation, small molecules below the renal threshold (45 to 60 kDa) are rapidly excreted, whereas the larger molecules are retained for varying periods of time, depending on their size and ease of enzymatic breakdown. MW is therefore an important determinant for the intravascular retention time of colloids. Notably, osmotic effectiveness depends on the number of particles, and not upon the molecular size. Therefore, the excretion of smaller particles continuously reduces the osmotic effectiveness of the infused solution. This is compensated for by the continuous supply of oncologically active molecules arising from the degradation of larger fragments.

The third number describes the degree of molar substitution (MS). Different generations of starches are named according to their degree of MS. Hetastarches refer to a MS of 0.7, hexa- and penta-starches refer to a MS of 0.6, 0.5 and 0.4, respectively. HES have a varying number of hydroxyethyl residues attached to the glucose particles within the starch polymer. The MS indicates the average number of hydroxyethyl residues per glucose subunit. As an example, the number 0.4 in the description of a HES preparation indicates that there are four hydroxyethyl residues per 10 glucose subunits. Substitution of –OH-groups with hydroxyethyl residues increases the solubility of the starch in water, and sterically inhibits the enzymatic breakdown of the starch polymer by amylase. Therefore, hydroxyethylolation prolongs the intravascular retention time.

Plasma accumulation was first reported by MISHLER et al. (8) after repetitive dosing of hetastarch in healthy volunteers. After three consecutive 30 g infusions of 6% HES 450/0.7, the residual HES plasma concentration 24 h after the final infusion was higher than the peak plasma concentration after the first infusion. LEHMANN et al. (7) investigated the low-molecular weight pentastarch 6% HES 70/0.5, and found plasma accumulation similar to the one reported by ASSKALI and FORSTER (9) for 6% HES 200/0.5 after repetitive use in volunteers for 5 days. This demonstrates that vascular retention apparently depends more on MS than on MW.

The pattern of hydroxyethylolation (MS) has also a significant impact on pharmacokinetic properties. Hydroxyethyl groups at the C₆ carbon atom inhibit the access of α-amylase to the substrate more efficiently than hydroxyethyl groups at the C₂ position (10). Hence, HES products with high C₆/C₄ ratios are expected to be degraded more slowly.

![Fig. 1. — Hydroxyethyl substitution of hydroxyethyl starch (HES) glucose subunits takes place preferentially at the C₆ and C₄ positions.](image)

TREIB et al. (11) compared two pentastarches (10% HES 200/0.5), differing only in their C₆/C₄ ratios. HES-plasma concentrations were lower from day 3 onwards in the group receiving HES with the lower C₆/C₄ ratio, and the in vivo MW in plasma decreased much more with this HES solution.

The third generation of HES, the tetraastarches, was developed with lower MS (0.4) to enhance degradation and to minimize retention in the circulation and tissues (12). Several dosing studies show that the clearance of tetraastarch (10% HES 130/0.4) (13) is at least 23 times higher than the
 Composition and official prices of different fluid solutions marketed in Belgium

<table>
<thead>
<tr>
<th></th>
<th>Voluven&lt;sup&gt;®&lt;/sup&gt; Waxy maize HES 6% 130/0.40</th>
<th>Volulyte&lt;sup&gt;®&lt;/sup&gt; Waxy maize HES 6% 130/0.42</th>
<th>Tetraspan&lt;sup&gt;®&lt;/sup&gt; Potato HES 6% 130/0.42</th>
<th>Glucose 5%</th>
<th>Ringer’s lactate</th>
<th>Plasmalyte&lt;sup&gt;®&lt;/sup&gt;</th>
<th>Hartmann&lt;sup&gt;®&lt;/sup&gt;</th>
<th>NaCl 0.9%</th>
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<tbody>
<tr>
<td>Sodium&lt;sup&gt;+&lt;/sup&gt;</td>
<td>154</td>
<td>137</td>
<td>140</td>
<td>0</td>
<td>130</td>
<td>140</td>
<td>130.5</td>
<td>154</td>
</tr>
<tr>
<td>Potassium&lt;sup&gt;+&lt;/sup&gt;</td>
<td>0</td>
<td>4</td>
<td>4.0</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>5.36</td>
<td></td>
</tr>
<tr>
<td>Chloride&lt;sup&gt;+&lt;/sup&gt;</td>
<td>154</td>
<td>110</td>
<td>118</td>
<td>0</td>
<td>109</td>
<td>98</td>
<td>111.7</td>
<td>154</td>
</tr>
<tr>
<td>Calcium&lt;sup&gt;+&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>2.5</td>
<td>0</td>
<td>1.5</td>
<td>0</td>
<td>1.84</td>
<td>0</td>
</tr>
<tr>
<td>Magnesium&lt;sup&gt;+&lt;/sup&gt;</td>
<td>0</td>
<td>1.5</td>
<td>1.0</td>
<td>0</td>
<td>1.5</td>
<td>0</td>
<td>1.84</td>
<td>0</td>
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<tr>
<td>Lactate&lt;sup&gt;+&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>28</td>
<td>0</td>
<td>27,8</td>
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<tr>
<td>Acetate&lt;sup&gt;+&lt;/sup&gt;</td>
<td>0</td>
<td>34</td>
<td>24</td>
<td>0</td>
<td>0</td>
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<td>Malate&lt;sup&gt;+&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>5</td>
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<td>0</td>
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<tr>
<td>Gluconate&lt;sup&gt;+&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>28</td>
<td>0</td>
<td>27</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Glucose&lt;sup&gt;+&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Osmolarity (mOsm/l)</td>
<td>308</td>
<td>286.5</td>
<td>296</td>
<td>278</td>
<td>273</td>
<td>295</td>
<td>278</td>
<td>308</td>
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<td>pH</td>
<td>4.5-5</td>
<td>5.7-6.5</td>
<td>5.6-6.4</td>
<td>3.5-6.5</td>
<td>6.5</td>
<td>6.5-8.0</td>
<td>5.0-7.0</td>
<td>4.5-7.0</td>
</tr>
<tr>
<td>Price (£/500ml)</td>
<td>9.24</td>
<td>9.5</td>
<td>9.5</td>
<td>1.52</td>
<td>1.24</td>
<td>7.19</td>
<td>1.87</td>
<td>1.41</td>
</tr>
</tbody>
</table>

Tetraspan<sup>®</sup>, NaCl 0.9%, Glucose 5%<sup>®</sup> and Hartmann<sup>®</sup> from B. Braun (Melsungen, Germany). Voluven<sup>®</sup> and Volulyte<sup>®</sup> from Fresenius-Kabi (Bad Homburg, Germany). Plasmalyte<sup>®</sup> from Baxter International (Deerfield, IL, USA).

<sup>+</sup> in mmol L<sup>-1</sup>

one of hexastarch (6% HES 200/0.62) (9) or heta-starch (6% HES 450/0.7), and almost five times as high as the one of pentastarch (10% HES 200/0.5) (8,9,13,14) in four healthy normal male volunteers following three consecutive daily 500 ml infusions (total 1500 ml). Accordingly, the maximum doses that may be administered to a patient during 24 hours are increasing with lower MS and lower concentration. These maximum doses amount 20 ml Kg<sup>−1</sup> d<sup>−1</sup> for 10% HES 200/0.5, 33 ml Kg<sup>−1</sup> d<sup>−1</sup> for 6% HES 200/0.5, and 50 ml Kg<sup>−1</sup> d<sup>−1</sup> for 6% HES 130/0.4 (15). Currently, only tetrastarches are commercially available in Belgium.

**Efficacy of HES: volume effects**

*Jacobs et al.* were one of the first to exactly quantify the volume effects of colloid infusions in patients (16) acute normovolemic hemodilution was performed to a hematocrit of 21% using 6% HES 130/0.4 (Voluven). After removal of 1.431 ± 388 ml of blood in 10 patients undergoing radical hysterectomy, and simultaneous replacement with 1.686 ± 437 ml of 6% HES 130/0.4, for the purpose of normovolemic hemodilution, blood volumes were 218 ± 174 ml higher than before HES administration (105 ± 4%). Thirty minutes later, the volume effect of the colloid was 98 ± 12%. In contrast, the volume effect of crystalloids in healthy adults is much lower, insofar as one liter of Ringer’s lactate replaces blood losses only by 17 ± 10% (17).

Accordingly, in parturient women undergoing spinal anesthesia for caesarean section, crystalloid “pre-loading” (i.e., administration before the induction of spinal anesthesia) has been repeatedly found to be much less effective in preventing hypotension than colloid pre-loading (18). On the other hand, “co-loading” (i.e., administration at the time of induction of spinal anesthesia) with HES is not more effective than co-loading with equal amounts crystalloids (19).

Whether the reduction in total volume of fluid required to achieve hemodynamic optimization using HES over crystalloid results in clinical benefit in colorectal surgery was investigated by YATES et al. (20). The authors randomly assigned 202 medium to high-risk patients undergoing elective colorectal surgery to receive either 6% HES 130/0.4 or balanced crystalloid for hemodynamic optimization. Subjects in the crystalloid group received more fluid [median (inter-quartile ranges) 3,175 (2,000-3,700) as compared to 1,875 (1,500-3,000) ml, *P* < 0.001] and had a higher 24 hour fluid balance [+4,226 (3,251-5,779) as compared to +3,610 (2,443-4,519) ml, *P* < 0.001]. No difference was seen in the number of patients who suffered from GI morbidity on postoperative day 5 [30% in the HES group and 32% in the crystalloid group; adjusted odds ratio = 0.96 (0.52-1.77)]. There was

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also no between-group difference in the incidence of postoperative complications.

As reported by Chappell et al., both intact endothelial glyocalyx and tight junctions between endothelial cells guarantee the retention of colloids, whereas the disruption of the glyocalyx (“capillary leak”) in various pathological conditions permits the extravasation of them (21, 22). In this case, the volume of colloid required for the achievement of hemodynamic resuscitation goals increases and approaches the amount of fluid needed when resuscitation is primarily performed with crystalloid solutions (21). In the ‘Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis’ (VISEP) trial, the differences between the hemodynamic effects of 10% HES 200/0.5 and those of Ringer’s lactate in 537 patients with severe sepsis were only minor (4). These findings were confirmed by the ‘Scandinavian Starch for Severe Sepsis/Septic Shock’ (6S) trial, which did not observe significant differences in fluid volumes needed for hemodynamic stabilization of the two study groups treated with either HES 130/0.4 or Ringer’s acetate (23). In a sequential study including more than 1,000 patients with severe sepsis, shock reversal was achieved equally fast with HES and crystalloids (24). More fluid was however needed over the first 4 days in the crystalloid group (crystalloids to hydroxethyl starch ratio = 1.4:1).

These findings are contrasted by the ‘CRYSTalloids Morbidity Associated with severe Sepsis’ (CRYSTMAS) study that compared HES 130/0.4 with 0.9% saline in patients with sepsis (5). Significantly less HES than saline was used to reach hemodynamic stabilization [1,379 ± 886 ml in the HES group and 1,709 ± 1,164 ml in the saline group (Mean difference = -331 ± 1,033, 95% CI -640 to -21), P = 0.0185]. Of note, the mean difference in the administered volume was much lower than what would have been expected from the above-mentioned data on volume effects in patients without a capillary leak (16). Hence, the CRYSTMAS study also clearly demonstrates a remarkable loss of efficacy of HES solutions in septic patients. The ‘Crystalloid Versus Hydroxyethyl Starch Trial’ (CHEST-trial), comparing a maize-derived 130/0.4 tetrastarch to 0.9% sodium chloride (saline) in 7,000 patients who had been admitted to intensive care units in Australia and New Zealand, found that, during the first 4 days after resuscitation, the HES group received significantly less study fluid than the saline group [mean (± SD) daily average, 526 ± 425 ml as compared to 616 ± 488 ml; P < 0.001], with most of the volume administered during the first 24 hours. The HES group also received significantly less non-study fluid than the saline group (851 ± 675 ml as compared to 1115 ± 993 ml; P < 0.001), resulting in a significantly lower positive net fluid balance (921 ± 1,069 ml as compared to 982 ± 1,161 ml, P = 0.03) (6).

**SAFETY of HES: Mortality, Renal Adverse Effects, Bleeding, Pruritus, Anaphylactoid Reactions**

Adverse effects of colloids are mainly due to the extravasation of the osmotically active macromolecules into the extravascular compartment once endothelial integrity is disrupted (21). Systemic inflammation, such as the one induced by sepsis, surgical trauma, cardiopulmonary bypass or major injuries, increases endothelial permeability (22). Moreover, it has recently been demonstrated that the induction of hypervolemia by preoperative volume loading in healthy individuals, or liberal perioperative fluid management also allows extravasation of colloids through disrupted endothelial glyocalyx (25).

**Mortality**

Concern is growing regarding possible excessive mortality when using HES preparations in critically ill patients (26). Different studies assessed the effect of HES on mortality. Intensive care unit mortality was higher among HES recipients in both the observational ‘Sepsis Occurrence in Acutely Ill Patients’ (SOAP) [odds ratio (OR) 1.82; CI, 1.51-2.19] and ‘Crystalloids or Colloids’ (CRYCO) (adjusted OR 1.76; CI = 1.00-3.11) studies (27,28).

In 2009, Schabinski et al. investigated the effects of a predominantly HES-based and predominantly non-HES-based fluid therapy on renal function in surgical ICU patients in a ‘before-after’ retrospective study (29). Although not being the primary outcome parameter, this study found that ICU hospital mortality rates were more than two times higher in patients who had received cumulative amounts of HES or gelatin solutions in the highest quartile (more than 33 ml Kg⁻¹ body weight of gelatin, and more than 33 ml Kg⁻¹ body weight of HES) than in other patients. It has to be noted, however, that the non-randomized approach of this study resulted in differences in the baseline characteristics between the two study groups. Moreover, the results of this study may also simply reflect disease severity, as it can be postulated that patients with more severe shock, and hence with

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higher mortality risk, may have required larger amounts of fluids.

Results from prospective, randomized controlled trials are contradictory. In the VISEP-trial, the rate of death at 28 days did not differ significantly between the HES group and the Ringer’s lactate group (26.7% and 22.1%, respectively; $P = 0.48$) (4). However, there was a trend towards an increased rate of death at 90 days in the HES group (41.0% as compared to 33.9%, $P = 0.09$) (Table 2). Moreover, in a post hoc univariate analysis, there was a direct correlation between the cumulative dose of HES and the rate of death at 90 days. In contrast, there was no corresponding correlation with the cumulative dose of Ringer’s lactate. It has to be noted though that a corresponding correlation with the cumulative dose of Ringer’s lactate. It has to be noted though that a

In contrast, the CHEST-trial, found no impact of HES on 90-day mortality (6) (Table 2).

Of note, the majority of the above-mentioned studies have been criticized for suffering from several methodological limitations, such as the inclusion of patients only after the initial stabilization phase, lack of valid resuscitation endpoints or resuscitation protocols, and failure to use pre-specified treatment algorithms.

Recently, the ‘Colloids Versus Crystalloids for the Resuscitation of the Critically Ill’ (CRISTAL) trial investigated death incidence within 28 days when receiving colloids (gelatins, dextrans, HES and albumin) or crystalloids (isotonic or hypertonic saline or Ringer’s lactate solution) (30). This mult-center trial stratified by case mix (sepsis, trauma or hypovolemic shock without sepsis, or trauma), and recruited 2,857 ICU patients. Within 28 days, there were 359 deaths (25.4%) in the colloid group as compared to 390 deaths (27%) in the crystalloids group (RR 0.96; 95% CI = 0.88 to 1.04; $P = 0.26$). Of note, 90-day mortality was lower among patients receiving colloids (RR 0.92; 95% CI = 0.86 to 0.99; $P = 0.03$). This trial is characterized by some noteworthy aspects that clearly distinguish the CRISTAL trial form other HES trials. The study patients had to have received no prior fluids for resuscitation during their ICU stay. Patients were only eligible when requiring fluid resuscitation for acute hypovolemia as defined by the combination

<table>
<thead>
<tr>
<th>Trial</th>
<th>VISEP (4)</th>
<th>6S trial (23)</th>
<th>CHEST (6)</th>
<th>CRISTMAS (5)</th>
<th>CRISTAL (30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of included patients</td>
<td>537</td>
<td>804</td>
<td>7000</td>
<td>196</td>
<td>2857</td>
</tr>
<tr>
<td>Disease condition</td>
<td>Severe sepsis</td>
<td>Severe sepsis</td>
<td>ICU admission requiring fluid resuscitation</td>
<td>Severe sepsis</td>
<td>Sepsis, trauma, hypovolemic shock</td>
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<tr>
<td>Mortality of control group (%)</td>
<td>33.9</td>
<td>43</td>
<td>17</td>
<td>34</td>
<td>34.2</td>
</tr>
<tr>
<td>Starch solution</td>
<td>10% 200/0.5</td>
<td>6% 130/0.42</td>
<td>6% 130/0.4</td>
<td>6% 130/0.4</td>
<td>Any colloid solution</td>
</tr>
<tr>
<td>Comparator</td>
<td>Ringer’s lactate</td>
<td>Ringer’s acetate</td>
<td>Saline</td>
<td>Saline</td>
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<tr>
<td>Carrier solution</td>
<td>Saline</td>
<td>Ringer’s acetate</td>
<td>Saline</td>
<td>Saline</td>
<td>Isotonic or hypertonic saline, buffered solutions</td>
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<tr>
<td>Renal replacement therapy (RR)</td>
<td>1.66*</td>
<td>1.35*</td>
<td>1.21*</td>
<td>1.83</td>
<td>0.93</td>
</tr>
<tr>
<td>Doubling of plasma creatinine (RR)</td>
<td>1.53*</td>
<td>1.18</td>
<td>/</td>
<td>1.22</td>
<td>/</td>
</tr>
<tr>
<td>Receiving RBC (RR)</td>
<td>1.12*</td>
<td>1.28*</td>
<td>/</td>
<td>1.39</td>
<td>/</td>
</tr>
<tr>
<td>Adverse events* (RR)</td>
<td>1.05</td>
<td>1.56</td>
<td>HES 5.3% vs. saline 2.8%, $P&lt;0.001$</td>
<td>1.16</td>
<td>/</td>
</tr>
<tr>
<td>90-Day mortality (RR)</td>
<td>1.21</td>
<td>1.17*</td>
<td>1.06, 95% CI 0.96 to 1.18; $P=0.26$</td>
<td>1.20</td>
<td>0.92*</td>
</tr>
</tbody>
</table>

RR, Relative risk. RBCs, red blood cells
*These relative risks differed from 1.00 with statistical significance at the 5% level.
*The definition of adverse events varied between the RCTs.
of hypertensive, evidence for low filling pressures, and low cardiac index as assessed either invasively or noninvasively, and when presenting signs of tissue hypoperfusion or hypoxia (30). Treatment assignment was then continued during the entire ICU stay. Unfortunately, the use of trial fluids was NOT blinded, so that a potential bias cannot be excluded. Moreover, the study only compared the 2 classes of fluids (colloids as compared to crystalloids), and not any specific agent. Last, the apparent benefit of colloids at 90 days should be interpreted with caution (31). 90-day mortality was a secondary outcome variable, with the confidence intervals approximating 1.0. Any interpretation that colloids decrease long-term mortality would therefore need validation in another trial.

Unfortunately, the evidence from meta-analyses is inconclusive as well. In 2013, Zarychanski et al. published a systematic review and meta-analysis (32) in critically ill surgical and medical adult patients, treated in an emergency or intensive care setting, and requiring volume resuscitation (a total of 10,290 patients were included, meaning from 38 eligible trials). After exclusion of 7 trials performed by an investigator whose research had been retracted because of scientific misconduct, this meta-analysis showed that the use of HES was associated with a significantly increased risk of mortality among 10,290 patients (RR 1.09; 95% CI = 1.02 to 1.17; F 0%; AR 1.51%; 95% CI = 0.02 to 3.00%). Likewise, a Cochrane analysis reviewed 25 randomized controlled trials of HES compared to crystalloids in 9,147 patients requiring volume replacement, and found that the use of HES might increase mortality (pooled RR 1.10; 95% CI = 1.02 to 1.19, p = 0.015) (33). In contrast, another meta-analysis evaluated the safety of tetrastarches in the context of elective and emergency surgery, trauma, and burns, and assembled the results of 21 studies (34). The mortality in the group of 1,918 randomly allocated patients amounted 11 over 956 patients having received tetrastarches [1.15% (95% CI = 0.57%-2.05%)] and 22 over 982 patients having received the comparator [2.24% (1.41%-3.37%)]. The OR for mortality for HES administration compared to all comparators was 0.51 (0.24-1.05; P = 0.079).

The systematic review and meta-analysis of Gillies et al. investigated the incidence of postoperative death with 6% HES solutions or alternative fluids in patients undergoing surgery with the exception of neurosurgery, transplantation, burns or obstetric surgery (35). In total, 1,567 patients were included in the analysis. There was no difference in hospital mortality (P = 0.91, F = 0%; RD = 0.00, 95% CI = -0.02-0.02). Subgroup analysis of 872 cardiac surgical patients from 10 studies also did not demonstrate any difference (P = 1.0, F = 0%; RD = 0.00, 95% CI = -0.02 to 0.01). The authors concluded that, due to the low event rates of death in this population, a very large randomized trial of 6% HES solutions would be required to demonstrate either significant benefit or harm associated with the use of HES-solutions in surgical patients. They also concluded that “given the absence of demonstrable benefit, the clear risks in critically ill patients, and the additional cost over more widely used fluids, we are unable to recommend routine clinical use of 6% HES solution in surgical patients.”

In 2012, a task force of the European Society of Intensive Care Medicine assembled consensus recommendations, based on the available evidence for the safety and efficacy of the currently most frequently used colloids (36). This task force recommends not to use HES with a MW equal of higher than 200 kDa, and/or a MS higher than 0.4 in patients with severe sepsis. They suggest that HES 130/0.4 should be used in patients with severe sepsis only in the context of clinical trials. Of note, other authors have heavily criticized these recommendations. Zacharowski et al. questioned the basis on which the task force was selected, and doubted whether the recommendations given by the expert group are supported by the majority of European intensive care specialists, or whether they merely reflect the ‘expert opinion’ of eight authors (37). Later in 2012, however, the Surviving Sepsis Campaign (SSC) also recommended not to use any hydroxyethyl starches for fluid resuscitation in patients with severe sepsis/septic shock (38). For the intra-/perioperative setting, no evidence-based guidelines are available.

Renal adverse effects

Concerns about the possible deleterious effects of HES on renal function were first raised by Legendre et al. in a retrospective study investigating the association between HES exposure of kidney donors and the subsequent renal storage of HES molecules in the recipients (39). The authors retrospectively compared the occurrence of osmotic nephrosis in patients who underwent kidney transplantation during 1990, when HES was rarely used for fluid resuscitation (group I, n = 51) and during 1992 (group II, n = 39), when HES was widely administered. The frequency of osmotic-nephrosis-like lesions was significantly higher in
group II than in group I (80% as compared to 14%, p < 0.01). Thereafter, numerous studies investigated the effects of colloids on renal function (40). In 2006, a systematic review of 23 RCTs and non-randomized studies documented adverse renal effects of HES, gelatin and dextran, whereas albumin was found to be renoprotective (41).

In 2008, the VISEP trial had to be stopped for safety reasons, insofar as after the first planned interim analysis, an increased rate of renal failure and death at 90 days in the group receiving 10% HES 200/0.5 had been observed (4) (Table 2). Comparable to the above-mentioned effects on mortality, there was a direct correlation between the cumulative dose of HES and the need for renal-replacement therapy, whereas no corresponding correlation with the cumulative dose of Ringer’s lactate could be demonstrated. The increased need for renal-replacement therapy in critically ill patients resuscitated with HES was also observed in the 6S-trial, a multicenter, parallel group, blinded study with 804 included patients. In the 90-day period, 22% of patients assigned to HES 130/0.42 were treated with renal-replacement therapy, as compared to 16% of patients assigned to Ringer’s acetate (23). Likewise, the CHEST-trial found that renal replacement therapy had to be instituted more frequently in patients receiving resuscitation with HES when compared to 0.9% NaCl (6).

Paradoxically, the incidence of renal injury (as defined by the Risk-Injury-Failure-Loss-End-stage kidney disease [RIFLE!] criteria) was higher in the saline group. On the other hand, post hoc analysis showed that, during the first 7 days, serum creatinine levels were significantly increased and urine output was significantly decreased in the HES group. Shaw and Kellum theorize that this paradox may be explained by a reduction in glomerular filtration rate by HES, despite an increase in early urine output, probably owing to more effective volume expansion with the colloid (42).

In contrast, the Crystalloids Morbidity Associated in Severe Sepsis (CRYSTMAS) study investigators assessed the safety of 6% hydroxyethyl starch 130/0.4 compared to 0.9% NaCl in 176 patients with severe sepsis (5). Acute renal failure occurred in 24.5% and in 20% of patients for HES and NaCl, respectively (P = 0.454).

The CRISTAL study did not show any evidence of colloid-related increase in the risk of RRT (30). These findings are in contrast to previous reports showing increased incidence of acute kidney injury following the administration of HES (4, 6, 23, 32, 33). The authors suggest 3 potential explanations for this discrepancy: first, the dose of HES used in the trial never exceeded the dose recommended by regulatory agencies, and patients with severe chronic renal failure were excluded. Second, the use of colloids was associated with a significant reduction in cardiovascular and respiratory failures, and third, the vast majority of patients in the crystalloid group received a chloride-rich solution (that is normal saline). Chloride-rich solutions might have increased the risk of kidney injury when compared with a chloride-restricted fluid therapy (43).

In a recent meta-analysis, ten trials reported the incidence of renal replacement therapy in 9,258 patients (32). Pooled results demonstrate a significant relationship between HES administration and risk of receiving renal-replacement therapy (RR = 1.32; 95% CI = 1.15-1.50; AR = 3.12%; 95% CI = 0.47-5.78%) when compared with other fluids. Five trials including 8,725 patients reported a higher incidence of acute renal failure for patients receiving HES (RR = 1.27; 95% CI = 1.09-1.47; AR = 5.45%; 95% CI = 0.44-10.47%). Although the CHEST-trial alone accounts for 35% of the weighting, its exclusion neither influences the direction nor the significance of the study findings.

Of note, different clinical conditions could result in differing safety data for HES. In a random cohort study in cardiac surgery, Rioux et al. demonstrated, for pentastarch 10% (250 kDa/0.45; given until the end of the first postoperative day), a dose-dependent risk of acute kidney injury (44). The authors suggest caution when using HES preparations in cardiac surgery. Another observational study with 238 cardiac surgery patients found HES 450/0.7 exposure to be a dose-related independent risk factor for impaired glomerular filtration rate (45). In contrast, a pilot study investigating the use of starch solutions (10% HES 250 kDa/0.5 versus crystalloids (0.9% saline) after cardiac surgery found no difference in daily creatinine levels, development of RIFLE risk criteria during hospital stay, or new dialysis (46). When focusing on tetrastarches, a recently published meta-analysis including 38 trials found no indications that the use of modern starches during surgery induces adverse renal effects as assessed by serum creatinine or the need for renal replacement therapy (34). Accordingly, a meta-analysis of 17 randomized studies evaluated renal safety of waxy maize-derived hydroxyethyl starches 130/0.40 and observed no evidence for renal dysfunction in 1,230 patients undergoing various surgical procedures (47). These results were confirmed by a recent systematic review and meta-analysis that showed no difference in the occurrence.
of author-defined acute kidney injury, and the use of RRT in a total of 401 and 445 patients, respectively (35). Subgroup analyses of patients undergoing cardiac and non-cardiac surgery, and of patients receiving tetrastarch solutions only showed similar findings.

Special attention should be paid to the use of HES in patients undergoing renal transplantation. As mentioned before, Legendre et al. were, in 1993, the first to notice osmotic-nephrosis-like lesions in kidney transplantation patients. Those lesions were noticed after a change in plasma volume expanders to HES (39). Subsequent studies proved that used HES as a plasma-volume expander in brain-dead donors impairs immediate renal function in kidney-transplant recipients (48). Contrarily, in a single-centre retrospective cohort study comparing HES and crystalloids, infusion of low molecular weight 6% HES 130/0.4 during and after renal transplantation was found to have no significant negative effect upon the rate of delayed graft function in 113 patients who underwent renal transplantation (49). However, this study apparently suffers from a lack of power to adequately address effects on delayed graft function, which occurs only infrequently.

Based on the current evidence, the European Society of Intensive Care Medicine task force recommends not using HES with a molecular weight higher than 200 kDa and/or a degree of substitution higher than 0.4 in patients with an increased risk of acute renal injury (36). They suggest that HES 130/0.4 be used in ICU patients with increased risk for acute kidney injury only in the context of clinical trials rather than in routine clinical practice. For the intraoperative use, no specific guidelines are available.

Impairment of coagulation

Bleeding associated with the administration of HES solutions has been widely reported. In the VISEP trial, patients in the HES group had a lower median platelet count (179,600 mm\(^3\); interquartile range = 122,000-260,000) than those in the Ringer’s lactate group (224,000 mm\(^3\); interquartile range = 149,800-314,800; P < 0.001), and received more units of packed red blood cells than patients in the Ringer’s lactate group (4). The 6S trial evaluated the incidence of bleeding in a 90-day period and found no significant differences between the two groups. 10% of patients assigned to HES 130/0.42 had severe bleeding as compared to 6% of patients assigned to Ringer’s acetate (RR = 1.52; 95% CI = 0.94-2.48; P = 0.09) (23). However, more patients in the starch group than in the Ringer’s acetate group received blood products (RR = 1.20; 95% CI = 1.07-1.36; P = 0.002), including packed red blood cells (RR = 1.28; 95% CI = 1.12-1.47; P < 0.001). The CHEST study also reported a significantly higher use of blood products in the HES group than in the saline group (78 ± 250 ml as compared to 60 ± 190 ml, P < 0.001) (6).

Bleeding complications are particularly frequently observed in the setting of cardiac surgery, and result in an increase in the use of blood products, morbidity, mortality, as well as cost of care. In 2001, Wilkes et al. compared cumulative blood loss during the first 24 hours after cardiopulmonary bypass when patients were exposed either to albumin or HES 450/0.7, and HES 200/0.5. Insufficient data were available for hydroxyethyl starch 130/0.4 versus albumin. However, no significant differences were detected in head-to-head comparisons of hydroxyethyl starch 130/0.4 with 200/0.5. (50). Sixteen trials involving 653 randomized patients were included in this meta-analysis. Postoperative blood loss was found to be significantly lower in patients exposed to albumin than in patients exposed to HES. Likewise, in systematic reviews comparing the safety of different colloids, the incidence of coagulopathy and clinical bleeding in cardiac surgical patients has been repeatedly shown to be increased with administration of HES (40).

The first RCT that directly compared the new-generation 6% HES 130/0.4 (Voluven\textsuperscript{®}) and 5% human albumin against Ringer’s lactate for fluid management during cardiac surgery was a study by Skchirtladze et al. in 2013 (51). The investigators randomly assigned 240 patients undergoing elective cardiac surgery to receive up to 50 ml Kg\(^{-1}\) day\(^{-1}\) of 5% albumin, HES, or Ringer’s lactate as the main infusion fluid, peri-operatively. Chest tube drainage over 24 hours – the primary study endpoint – did not differ significantly between the groups (P = 0.085). There was, however, a significant group difference in the quantity of blood transfusion (P = 0.0004). Patients in the Ringer’s lactate group received fewer packed red blood cells as compared with patients in the human albumin group (P = 0.0015) and HES (P = 0.0002). The difference in transfusion requirements in this trial can be explained either by the negative impact of the two colloids on blood coagulation – both colloids affected clot formation and clot strength – but also by the more profound hemodiluting effect, which decreased hemoglobin levels below values of 7.0 and 8.9 g dl\(^{-1}\) more promptly, which were the triggers to ad-
minister packed red blood cells during and after cardiopulmonary bypass, respectively.

These findings are contradictory to the above-mentioned meta-analysis of Van der Linden et al., who investigated the effects of modern starches also on coagulation (34). In summary, 38 studies were found to evaluate the effects of tetrastarches on blood loss in patients undergoing cardiovasculare, major abdominal, or orthopedic surgery. Among these studies, 1,602 patients received a tetrastarch solution, and 1,678 another colloid or crystalloid solution. This meta-analysis could not find an increase in perioperative blood loss, in the amount of allogeneic blood transfused, or in the exposure to allogeneic blood products in patients receiving tetrastarches, as compared with those receiving other colloids or crystalloids. It has to be mentioned, though, that the included studies varied markedly in their protocol, design and objectives.

As for patients with increased risk for renal failure, the ESICM task force suggests that HES 130/0.4 should be used in patients with increased risk of bleeding only in the context of clinical trials, rather than in routine clinical practice (36).

**Pruritus**

HES-related pruritus has been systematically described only since the early 1990s (52). Its delayed recognition as a clinical entity appears to be at least partly due to the considerable delay in the onset of symptoms, in many cases occurring only after discharge from the hospital. Pruritus was initially reported in otologic patients receiving relatively high doses of hyperoncotic HES to improve microcirculation (52). HES-associated pruritus typically manifests as pruritic crises, prompting patients to seek medical attention and seriously impairing quality of life. In one study in critically ill patients, the 44% who developed pruritus even experienced a severe, persistent, and refractory form of this condition (53). HES is deposited in a variety of tissues, including skin, liver, muscle, spleen, intestine and others, in a dose-dependent and time-related manner (54,55). Of note, neither the molecular weight nor the molar substitution of HES seems to exert a statistically significant effect on the occurrence of pruritus (Table 3) (40).

**Anaphylactoid reactions**

In 2004, a systematic review described the incidence of anaphylactoid reactions induced by artificial colloids when compared to albumin (40). The pooled incidence of anaphylactoid reactions after albumin administration was 9.44 per 10^5 infusions. Infusions of HES, gelatin and dextrane were associated with a significantly increased incidence of anaphylactoid reactions (Table 4). Administration of HES more than quadrupled the incidence of anaphylactoid reactions. Since 2004, there are no recent data available that could allow a re-evaluation of anaphylactic reactions along with colloid administration.

**Table 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pooled Odds Ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>HES exposure (HES vs. no HES)</td>
<td>1.78</td>
<td>1.23 - 2.58</td>
</tr>
<tr>
<td>HES dose (per 100-g increment)</td>
<td>1.46</td>
<td>1.38 - 1.55</td>
</tr>
<tr>
<td>Molecular weight of HES (450 kDa vs 200 kDa)</td>
<td>1.32</td>
<td>0.55 – 3.16</td>
</tr>
<tr>
<td>Molar substitution ratio of HES (≤ 0.5 vs. &gt; 0.5)</td>
<td>1.19</td>
<td>0.54 – 2.60</td>
</tr>
</tbody>
</table>

**Table 4**

<table>
<thead>
<tr>
<th>Colloid</th>
<th>Pooled Incidence Rate Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyethyl starch</td>
<td>4.51</td>
<td>2.06 - 9.89</td>
</tr>
<tr>
<td>Dextran</td>
<td>2.32</td>
<td>1.21 – 4.45</td>
</tr>
<tr>
<td>Gelatin</td>
<td>12.4</td>
<td>6.40 – 24.0</td>
</tr>
</tbody>
</table>

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Dependency of adverse effects and safety upon oncoticity, dose and origin of HES

Oncocity

The hypothesis that renal adverse effects of HES are evoked by hyperoncocity was evaluated in several studies. In 2010, a meta-analysis comparing hyperoncotic albumin and HES solutions found that hyperoncotic human albumin decreased the odds for acute renal injury, and improved survival, while hyperoncotic HES increased the risk of acute renal injury (56). It has to be noted, though, that five out of seven trials included patients with liver cirrhosis, in whom albumin was given for ascites with or without infection. An international prospective cohort study included 1,013 ICU patients needing fluid resuscitation for shock, but excluded patients suffering from cirrhosis or receiving plasma (28).

The use of artificial hyperoncotic colloids [OR = 2.48 (1.24-4.97)] and hyperoncotic albumin [OR = 5.99 (2.75-13.08)] was significantly associated with the occurrence of renal adverse events.

Based on previous evidence, the ESICM task force suggests to avoid using hyperoncotic solutions for fluid resuscitation outside the context of clinical trials (36).

Dose-dependency

Various systematic reviews and clinical studies suggest that the adverse effects of synthetic colloids, i.e., coagulopathy, renal impairment and HES-associated pruritus, are related to dosage (4, 28, 40, 44). In 2009, Schabinski et al. examined, in a retrospective study, the adverse renal effects of cumulative doses of either HES (130/0.4) or gelatin solutions in ICU patients (29). One of the main findings was that higher cumulative doses (over 33 ml Kg⁻¹ body weight) of either HES or gelatin solutions were associated with a higher risk of renal failure in the overall ICU population, and in patients with severe sepsis. This observation was in accordance with the findings of the prospective VISEP trial (4) that could clearly demonstrate an association between nephrotoxicity of HES, and the cumulative administered dose. Likewise, a dose-dependent risk of acute kidney injury was observed for pentastarch given until the end of the first postoperative day following cardiac surgery (44). The observed cutoff dose predicting acute renal injury was 14 ml Kg⁻¹. On the other hand, clinical studies analyzing the effects of lower doses of HES could not find an increased incidence of renal failure. For example, a retrospective study with 168 ICU patients who received 763 ± 593 ml HES 130/0.4 during the first 48 hours (corresponding to approximately 10 ml Kg⁻¹) (57) or an observational study where the median amount of HES per ICU patient was 1000 ml in 2 (1-3) days (approximately 15 ml Kg⁻¹ HES) (27) did not find such an association. For HES, recommended maximum daily doses range from 20-50 ml Kg⁻¹ body weight, depending on molecular weight and degree of substitution. The evidence having led to the dose limit of 50 ml Kg⁻¹ day⁻¹ for 6% HES 130/0.4 (as recommended by the manufacturer) is not clear. Therefore, the ESICM task force recommends a reassessment of the existing dose limits for HES (36).

Waxy maize versus potato-derived HES solutions

Modern third generation starches are derived from different source materials: waxy maize or potato. Waxy maize starch (HES 130/0.4) is largely (approximately 98%) composed of highly branched amylopectin, while potato starch (HES 130/0.42) is a heterogeneous mixture of approximately 75% amylopectin, and 25% linear chains of amylose. The degree of branching is therefore lower in potato starch (58). These and other structural differences, such as MS, C₃/C₆ ratio, and intrinsic viscosity may seriously affect pharmacokinetic properties. In this context, Lehmann et al. found significant differences in the total apparent clearance and a higher area under the plasma concentration curve for the waxy maize-derived product (HES 130/0.4), demonstrating that waxy-maize- and potato-derived starches are not bio-equivalent (59). Degradation and elimination should theoretically occur more rapidly in the polymer with the lower MS (i.e., the waxy maize-derived HES 130/0.4 product) but Lehmann suggested that the higher C₃/C₆ ratio of 9 : 1 hydroxyethylolation of waxy maize-derived starches at the second carbon atom (C₂) effectively inhibits access of a-amylase, thus retarding degradation. Of note, the 6S trial used a potato-derived HES-solution (Voluven®), while patients in the CHEST trial were randomized to the use of waxy maize-derived starch (Tetraspan®).

Conclusion

HES solutions are widely used in the perioperative setting with the aim to augment plasma...
volume. Although significantly more expensive than crystalloids (Table 1), HES enjoys a widespread use. There is a widespread belief that HES solutions exhibit more potent volume effects than crystalloids and hence allow reducing the total infused volume. However, this assumption has repeatedly been questioned by several clinical trials. Moreover, there is no convincing evidence that the use of HES solutions might translate into better outcomes. In contrast, several large-scale randomized controlled trials have raised serious concerns about the safety of hydroxyethyl starches (HES). The use of HES in critically ill patients has been shown to be associated with a higher incidence of renal injury or failure, a higher need for renal replacement therapy (RRT), and an increased mortality. These adverse effects have also been observed after the introduction of newer starch generations (with theoretically advantageous pharmacodynamic and pharmacokinetic properties).

Consequently, current guidelines clearly recommend against the use of HES in patients with sepsis, acute renal injury or at risk of, and potential bleeding problems.

On June 14th in 2013, the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC) has concluded that the benefits of HES solutions no longer outweigh their risks, and therefore recommended that the marketing authorizations for these medicines be suspended (1). The PRAC suggested that the suspension should remain in place unless the marketing authorization holder could provide convincing data to identify a group of patients in whom the benefits of the medicines outweigh their risks. Following the PRAC recommendation, some of the marketing-authorization holders requested a re-examination. On November 11th 2013, the PRAC concluded, in view of the available data, that the increased risk of mortality and RRT or renal failure associated with the use of hydroxyethyl starch containing medicinal products outweighs its limited clinical benefits in the approved indications, and in any patient population. It has to be noted though that the PRAC could not include the results of the CRISTAL study, which became available only after the publication of the PRAC statement. The PRAC recognizes that this new evidence could be of relevance. On June 24th in 2013, the U.S. Food and Drug Administration published a safety communication (http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm358349.htm) in which it was recommended (2):

- not to use HES solutions in critically ill adult patients including those with sepsis, and those admitted to the ICU
- to avoid use in patients with pre-existing renal dysfunction
- to discontinue use of HES at the first sign of renal injury
- to monitor renal function for at least 90 days in all patients
- to avoid use in patients undergoing open heart surgery in association with cardiopulmonary bypass due to excess bleeding
- to discontinue use of HES at the first sign of coagulopathy.

Concerning the perioperative administration of HES, high quality evidence is lacking, as well as large-scale randomized controlled trials. Results from trials in surgical patients are contradictory, which has been attributed to the inclusion of heterogeneous patient populations, different dose regimens, financial interests of the sponsor, small sample sizes, lack of blinding and allocation concealment, and a limited follow-up time (60). In addition, the true benefit of HES with respect to its volume effect is uncertain. The lack of clear evidence of harm in surgical patients presumably accounts for the FDA’s decision not to withdraw HES solutions completely in the USA (2); however, some have argued that the absence of a demonstrable benefit, combined with increased costs, is a strong reason to discourage HES-solutions use (33).

In contrast, on June 27th 2013, the Medicines and Healthcare Products Regulatory Agency (MHRA) announced the withdrawal of HES products from the United Kingdom, allowing 48 hours only to return all unexpired stocks (61).

In summary, it is at current impossible to give an evidence-based recommendation on the perioperative fluid resuscitation with HES. A cautious and restrictive use of HES in the perioperative period is warranted. A pragmatically and clinically oriented approach is shown in Box 1. Large-scale randomized controlled trials in perioperative patients are warranted.
Box 1: Standard operating procedure for the perioperative use of HES-solutions (Department of Anesthesiology, UZ Leuven)

Contraindications:

- HES solutions must no longer be used in patients with sepsis, burn injuries or critically ill patients.
- HES solutions are contraindicated in patients with renal impairment (eGFR < 85 ml min⁻¹; acute kidney injury (AKI) or chronic renal failure) or renal replacement therapy. The use of HES must be discontinued at the first sign of renal injury. Patients’ kidney function should be monitored after HES administration (determination of serum creatinine 24 hours after administration).
- Absolute increase in serum creatinin of ≥ 0.3 mg dl⁻¹ (≥ 26.4 μmol L⁻¹), or percentage increase in serum creatinine ≥ 50%, or reduction in urine output, defined as < 0.5 ml Kg⁻¹ h⁻¹ for more than 6 hours (unless caused by hypovolemia).
- 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.
- Further contraindications:
  - Intracranial or intracerebral bleeding
  - Hyperhydration, including patients with acute lung edema
  - Dehydration
  - Severe liver dysfunction

Indications:

Although there is a lack of convincing data on efficacy and safety, HES solutions may still be used for the treatment of acute hypovolemia. The following precautions should be taken in each individual patient (63):

1) HES solutions should only be used for the treatment of acute hypovolaemia due to acute blood loss, when crystalloids alone are not considered sufficient.
   - Hypovolemia due to bleeding should be confirmed by at least one of the following criteria:
     - Observed/witnessed acute blood loss
     - Positive test result for fluid responsiveness (passive leg raising test, ‘mini-fluid challenge’)
     - Lactate ≥ 3 mmol L⁻¹ (except in case of hepatic failure)
     - ScvO2 < 70 %, SvO2 < 65 % (except for anemic patients, or patients with heart failure)
     - Hypotension (systolic arterial blood pressure < 90 mmHg)
     - Oliguria (urine output < 0.5 ml Kg⁻¹ h⁻¹ over 6 h)

2) Use only last-generation HES solutions.
3) Start of HES-administration only during the acute phase (time interval < 6 h from the onset of shock).
4) Limit the administration of HES solutions to a maximum of 24 h.
5) HES solutions should be used at the lowest effective dose for the shortest period of time. Treatment should be guided by continuous haemodynamic monitoring so that the infusion is stopped as soon as appropriate haemodynamic goals have been achieved.
6) Respect maximal doses of HES solutions (e.g. 6% HES 130/0.4 30 ml Kg⁻¹ d⁻¹)
7) HES solutions can be used in the prevention of spinal-induced hypotension following spinal anesthesia in elective surgery provided that no contra-indications (as listed above) are present.

References

2. Food and drug administration. FDA safety communication: boxed warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings, 2013.

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15. As recommended by the manufacturer.


59. Lehmann G., Marx G., Forster H., Bioequivalence comparison between hydroxyethyl starch 130/0.42/6 and hydroxyethyl starch 130/0.4 6% and Ringer’s lactate on blood loss and coagulation after cardiac surgery, *Crit. Care*, 17, R166, 2013.