

# The Efficacy and Safety of Colloid Resuscitation in the Critically Ill

Christiane S. Hartog, MD, Michael Bauer, MD, and Konrad Reinhart, MD

Despite evidence from clinical studies and meta-analyses that resuscitation with colloids or crystalloids is equally effective in critically ill patients, and despite reports from high-quality clinical trials and meta-analyses regarding nephrotoxic effects, increased risk of bleeding, and a trend toward higher mortality in these patients after the use of hydroxyethyl starch (HES) solutions, colloids remain popular and the use of HES solutions is increasing worldwide.

We investigated the major rationales for colloid use, namely that colloids are more effective plasma expanders than crystalloids, that synthetic colloids are as safe as albumin, that HES solutions have the best risk/benefit profile among the synthetic colloids, and that the third-generation HES 130/0.4 has fewer adverse effects than older starches.

Evidence from clinical studies shows that comparable resuscitation is achieved with considerably less crystalloid volumes than frequently suggested, namely, <2-fold the volume of colloids.

Albumin is safe in intensive care unit patients except in patients with closed head injury. All synthetic colloids, namely, dextran, gelatin, and HES have dose-related side effects, which are coagulopathy, renal failure, and tissue storage. In patients with severe sepsis, higher doses of HES may be associated with excess mortality. The assumption that third-generation HES 130/0.4 has fewer adverse effects is yet unproven. Clinical trials on HES 130/0.4 have notable shortcomings. Mostly, they were not performed in intensive care unit or emergency department patients, had short observation periods of 24 to 48 hours, used cumulative doses below 1 daily dose limit (50 mL/kg), and used unsuitable control fluids such as other HES solutions or gelatins.

In conclusion, the preferred use of colloidal solutions for resuscitation of patients with acute hypovolemia is based on rationales that are not supported by clinical evidence. Synthetic colloids are not superior in critically ill adults and children but must be considered harmful depending on the cumulative dose administered. Safe threshold doses need to be determined in studies in high-risk patients and observation periods of 90 days. Such studies on HES 130/0.4 are still lacking despite its widespread and increasing use. Because there are safer and equally effective alternatives in the form of crystalloids, use of synthetic colloids should be avoided except in the context of clinical studies. (*Anesth Analg* 2011;112:156–64)

The debate whether critically ill patients should be resuscitated with crystalloids, colloids, or both has for many years been mainly a debate about effectiveness. Meta-analyses and recent studies in adults and children consistently concluded that colloids were not associated with an improvement in survival in the setting of intensive care or during surgery.<sup>1–6</sup> Mortality may not be the only outcome to assess whether colloids have an advantage over crystalloids. They might be expected to decrease morbidity, but recent large-scale clinical studies provided no indication of less hypotension, faster recovery, or shorter intensive care unit (ICU) or ventilator time.<sup>4,5</sup>

There is also the issue of safety. Several meta-analyses have identified an increased risk of death after use of colloids in general<sup>3,7,8</sup> or albumin specifically,<sup>9</sup> but the analyses were based on data of mostly small studies and heterogeneous

groups of patients. In 2004, the landmark SAFE trial compared albumin and normal saline in nearly 7000 intensive care patients with the intent to determine whether the claim of increased mortality associated with albumin administration was correct. The results showed that both fluids performed equally well. Except in patients with traumatic brain injury, albumin was as safe as normal saline.<sup>4</sup>

There are comparably fewer data to confirm the safety of synthetic colloids, including gelatin, dextran, and hydroxyethyl starch (HES). Synthetic colloids are popular in Europe<sup>10</sup> and HES has become one of the most frequently used colloidal plasma expanders worldwide.<sup>11,12</sup>

But what is the evidence from clinical trials to support widespread use of starches in the ICU and emergency setting? Recent meta-analyses have found that HES administration is associated with an increased risk of renal failure when given for acute intravascular volume depletion,<sup>13</sup> in critically ill patients,<sup>14</sup> and more specifically in patients with sepsis.<sup>15,16</sup> Moreover, one analysis confirmed a trend toward higher mortality rates in septic patients after the use of HES,<sup>14</sup> which was driven by the findings of one major sepsis trial.<sup>5</sup> However, it is suggested that third-generation starches are safer than older solutions.<sup>17</sup>

To bring more light into the crystalloid/colloid debate, it may be useful to look more closely at the rationales that support the current choice of colloids. We have identified 4 main arguments:

1. Colloids are more effective plasma expanders than crystalloids,

From the Department of Anesthesiology and Intensive Care Medicine, Friedrich-Schiller-University, Jena, Germany.

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Address correspondence and reprint requests to Prof. Dr. med. Konrad Reinhart, Department of Anaesthesiology and Intensive Care Medicine, Friedrich Schiller University, Erlanger Allee 101, D-07747 Jena, Germany. Address e-mail to konrad.reinhart@med.uni-jena.de.

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2. Synthetic colloids, i.e., dextran, gelatin, and HES are equally effective and safe but less costly than albumin,
3. HES solutions have the best risk/benefit profile among the synthetic colloids, and
4. The third-generation HES 130/0.4 is safer than older-generation HES solutions.

In the following text, we investigate the evidence base for these arguments and discuss them in the light of new evidence from recent clinical studies and meta-analyses.

## **(1) ARE COLLOIDS MORE EFFECTIVE PLASMA EXPANDERS THAN CRYSTALLOIDS IN THE CRITICALLY ILL?**

### **Achievement of Hemodynamic Goals**

Leading back to Starling's law of capillary circulation, colloids are able to increase plasma volume and increase the colloid oncotic pressure immediately after administration.<sup>18,19</sup> They are therefore considered superior to crystalloids for treating hypovolemia. However, this effect may be short-lived and of minor clinical relevance. A number of randomized clinical trials (RCTs) in critically ill adults and in children have now suggested that crystalloids are equally effective to achieve lasting resuscitation according to preset end points as colloids.<sup>4–6,20</sup>

In recent years, 3 major ICU trials have compared the effects of crystalloid and colloid resuscitation on outcomes. The SAFE trial compared albumin and normal saline in ICU patients, and the VISEP study looked at 10% HES 200/0.5 and Ringer lactate (RL) solution in 537 patients with severe sepsis. Both studies found that the end points 28-day mortality, ICU or hospital length of stay, number of organ failures, or duration of mechanical ventilation were not different between groups.<sup>4,5</sup> Wills et al.<sup>6</sup> compared dextran, HES, and RL in children with shock syndrome due to dengue fever and found that overall time to final cardiovascular stabilization was similar in all groups.

One would expect that hemodynamic variables in these studies were normalized more effectively by the colloid fluids. Indeed, the hematocrit in hypovolemic children was immediately reduced by dextran and HES to a greater degree (–25% and –22%, respectively) than by RL (–9%,  $P < 0.001$ ). However, after the initial 2 hours, hematocrit values rebounded in both colloid groups (+5%), but remained stable in the RL group (0%,  $P < 0.001$ ). The authors interpreted this as resulting from a secondary efflux of the macromolecules from the vasculature.<sup>6</sup> In adult patients, colloids achieved slightly, but significantly higher, central venous pressures, whereas mean arterial blood pressure or central venous oxygen saturation were equally high in the crystalloid groups.<sup>4,5</sup>

Upadhyay et al.<sup>20</sup> randomized 60 children with severe sepsis to receive either gelatin or normal saline to normalize mean arterial blood pressure or central venous pressure values. At the end of fluid resuscitation, plasma volume, total body water, extracellular fluid volume, and interstitial fluid volume were similar. The median time taken for fluid resuscitation was 45 (15–98) minutes in the saline group and 35 (15–90) minutes in the gelatin group ( $P = 0.41$ ) and

clinical outcomes (hemodynamic stability at 6 and 12 hours, number of organ failures, and survival rate) were similar.<sup>20</sup>

It seems, therefore, that hemodynamic changes by colloids are immediate effects that do not last and do not lead to improved clinical outcomes in comparison with crystalloids.

### **Risk of Edema Formation**

A side effect of resuscitation is edema formation. Crystalloids and colloids extravasate from the vasculature and albumin moves freely into the pulmonary interstitium.<sup>21</sup> These fluid movements have been interpreted in several ways. On one hand, colloid proponents have argued that colloids lessen the risk of edema because they increase intravascular colloid oncotic pressure, and on the other hand, crystalloid proponents have pointed out that colloids may increase the risk because they leak into the interstitium.<sup>21</sup> Previous literature reviews were not helpful because clinical studies had controversial results and severe methodological drawbacks.<sup>22</sup> There is now evidence from recent large-scale clinical trials that pulmonary function is not affected by fluid choice. Lung water, pulmonary sequential organ failure assessment score, ventilation times, and extravascular fluid volumes were comparable in adults and children with capillary leakage after administration of crystalloids or colloids.<sup>4,5,20,23,24</sup>

It has been suggested that HES possesses additional properties to “plug the leaks”<sup>25</sup> in states of capillary leakage, since Zikria et al.<sup>26</sup> first attributed a reduction of albumin leakage from standardized scald burns in rat jejunum after administration of HES with molecular weights (MWs) between 100 and 300 kDa to a hypothetical “sealing” effect of this compound. However, direct observation of fluorescein-isothiocyanate–marked HES with different MWs in a rat hemorrhage model using intravital microscopy showed that HES diffused into the surrounding tissue within seconds after administration.<sup>27</sup> In several elegant studies in patients with capillary leak, the Groeneweld group found that extravascular lung water and pulmonary edema were not different after administration of HES or crystalloids.<sup>23,24</sup>

It should also be pointed out that aggressive overresuscitation with crystalloids in trauma patients may result in increased incidence of brain edema and secondary abdominal compartment syndrome.<sup>28,29</sup> A positive fluid balance may be a strong prognostic risk factor for death.<sup>30</sup> However, aggressive resuscitation may also be a marker of illness severity rather than part of the causal chain for death, and overresuscitation can also occur with colloids. There is no clinical evidence to support the belief that colloids, over longer periods of time, result in a less positive fluid balance or improved clinical outcomes in critically ill or sepsis patients.

### **Crystalloid-Colloid Volume Ratio**

Resuscitation with crystalloids in critically ill patients requires more fluid volume,<sup>31</sup> and textbooks recommend a 3-fold or even higher ratio of crystalloid than colloid volumes to achieve resuscitation to comparable end points.<sup>32</sup>

However, direct comparisons in patients with capillary leak show that the ratio between required volumes in the crystalloid and colloid groups is in fact more in a range

between 1 and 2. In several thousand critically ill patients, the volume of normal saline needed for resuscitation on day 1 was only 1.3-fold larger than the volume of 4% albumin, and over the first 4 days, the ratio was 1.4.<sup>4</sup> In 537 septic patients, comparison of administered volumes of RL with 10% HES 200/0.5 yielded a volume ratio of 1.6 on the first day and 1.4 over the first 4 days.<sup>5</sup> In 383 children with dengue shock syndrome, hemodynamic stabilization was achieved with equal volumes of colloid and crystalloid,<sup>6</sup> and in 60 children with septic shock, the volume ratio of administered saline to 3.5% gelatin was 1.6.<sup>20</sup>

We identified 4 RCTs with crystalloid from recent systematic meta-analyses<sup>2</sup> and an extensive narrative review<sup>17</sup> that compared HES 130/0.4 with crystalloid. The studies used prespecified end points for fluid therapy in the perioperative setting of abdominal or cardiac surgery.<sup>33–36</sup> When total volumes between crystalloid and colloid groups were compared, ratios ranged between 2.1 and 1.6. Further and more systematic research is necessary to determine the relevance of this observation.

Recent experimental data confirm that the volume effect of crystalloid solution is not much less than that of oncotic solutions. In a porcine model of uncontrolled liver bleeding, the volume effect achieved by RL was 76% compared with 115% achieved by 6% HES 130/0.4, and less RL than HES was given (0.7:1) because 6 of 7 pigs stopped bleeding after RL.<sup>37</sup>

## **(2) ARE SYNTHETIC COLLOIDS EQUALLY EFFECTIVE AND SAFE AS HUMAN ALBUMIN?**

One conclusion drawn from the comparison of different fluids in the perioperative period is that starches can easily replace albumins as volume expanders because they are equally safe but less expensive.<sup>38</sup> However, recent meta-analyses failed to find a mortality benefit of any type of colloid in critically ill patients.<sup>2,39</sup> However, the paucity of data was generally deplored. Moreover, there is no evidence that the presumed additional benefits of starches over other colloids, which include antiinflammatory effects, improved microcirculation and tissue oxygenation,<sup>40</sup> or the above-mentioned “sealing” effect have improved mortality or morbidity in RCTs. On the contrary, animal studies have shown that starches exert proinflammatory actions on the kidney interstitium<sup>41</sup> and on thrombocytes.<sup>42</sup> Although there seems to be little difference between natural and synthetic colloids concerning their hemodynamic properties, albumin may indeed have some additional benefits in certain patient populations. In a subgroup of 1218 patients from the SAFE study with severe sepsis, albumin tended to decrease mortality (30.7% vs 35.3%,  $P = 0.09$ ) and did not increase rates of renal replacement therapy.<sup>43</sup> Children with severe malaria may have better survival rates after albumin than after nonalbumin control solutions according to the findings of a meta-analysis (odds ratio [OR], 0.19; 95% confidence interval [CI], 0.06–0.59).<sup>44</sup> In patients with spontaneous bacterial peritonitis complicating cirrhosis, fluid therapy with albumin was associated with less renal failure and reduced mortality.<sup>45</sup>

However, albumin may be harmful in patients with traumatic brain injury. The SAFE study showed that 28-day mortality in the subgroup of patients with trauma and an

associated brain injury was higher in the albumin than in the saline group (59/241 (24.5%) vs 38/251 (15.1%), RR 1.62, 95% CI, 1.12–2.34;  $P = 0.009$ ).<sup>4</sup> A post hoc follow-up analysis with 460 patients from this group confirmed that patients receiving albumin had a significantly higher 24-month mortality (33.2% vs 20.4%,  $P = 0.003$ ).<sup>46</sup>

## **(3) DO HES SOLUTIONS HAVE THE BEST RISK/BENEFIT PROFILE AMONG THE SYNTHETIC COLLOIDS?**

### **Side Effects of Synthetic Colloids**

All synthetic colloids carry inherent risks of anaphylactic reactions, coagulopathy, and renal impairment; however, there are few data to determine their relative safety.<sup>47</sup>

High-quality clinical trials have hitherto failed to show a benefit for any synthetic colloid over crystalloids or other colloids. All synthetic colloids are associated with a several-fold increased incidence of anaphylactoid reactions compared with albumin, with an incidence rate ratio of 4.51 (95% CI, 2.06–9.89) for HES, 2.32 (95% CI, 1.21–4.45) for dextran, and 12.4 (95% CI, 6.40–24.0) for gelatin.<sup>47</sup> In 1994, a prospective multicenter study found that HES had the lowest risk of anaphylactoid reactions among the synthetic colloids.<sup>48</sup> HES 450/0.7 and 200/0.5 administration increased bleeding when used during cardiac surgery<sup>49</sup> after which hetastarch received a warning label in the United States;<sup>50</sup> HES 200/0.6 was associated with fatal bleeding in patients with intracranial hemorrhage<sup>51</sup> and is no longer sold in France. HES 200/0.6 and HES 200/0.5 increased the frequency of renal failure in septic patients<sup>5,52</sup> and in renal transplants.<sup>53</sup> HES 250/0.45 was associated with increased acute kidney injury (AKI) in cardiac surgery.<sup>54</sup>

The mechanism of renal failure is not fully understood. It may include reabsorption of the macromolecule into renal tubular cells leading to osmotic nephrotic lesions or renal plugging due to hyperviscous urine.<sup>55</sup> In animal kidneys, administration of HES was associated with interstitial inflammation that was more marked after a 10% starch solution of higher MW.<sup>41</sup> Likewise, in a model of fulminant endotoxemia, 10% HES 200 had more early effects on renal variables within 12 hours than 6% HES 130 or crystalloid.<sup>56</sup> Schortgen et al.<sup>57</sup> have suggested that hyperoncotic solutions including dextrans, HES, or 20% albumin significantly increased the risk of renal adverse events occurrence in the ICU. HES tissue storage in cutaneous nerves can lead to pruritus<sup>58</sup> and higher cumulative doses may be responsible for extensive organ depositions with the appearance of a foamy macrophage syndrome.<sup>59</sup>

Gelatins, similar to starches, impair platelet function and reduce von Willebrand and coagulation factor VIII:c.<sup>60</sup> In patients with intracranial bleeding, 4% gelatin and 6% HES 200/0.5 increased blood transfusion requirement and inflammation markers and reduced cerebral autoregulation. Both synthetic colloids increased the risk for adverse clinical outcome in a dose-dependent manner (OR, 2.53/L/d;  $P = 0.025$ ).<sup>61</sup>

Gelatin may also be associated with renal impairment in patients at risk.<sup>62</sup> Change of standard colloid fluid from HES 130/0.4 to 4% gelatin in the ICU did not improve the incidence of renal failure in 205 patients with severe sepsis (35.6% and 36.1%, respectively); however, HES and gelatin



in doses  $>33$  mL/kg were associated with an increased incidence of renal failure (52.5% and 51.9% respectively) although patients who received higher doses of synthetic colloids had similar creatinine values and simplified acute physiology II scores at admission.<sup>63</sup> The need for renal replacement therapy (RRT) of 35.6% with HES and 36.1% with gelatin was surprisingly high in this study. RRT was needed by only 18.8% of patients in the crystalloid arm of the VISEP trial, likewise in the SAFE trial by only 18.2% and 18.7% of severe sepsis patients in the normal saline and human albumin arms, respectively.<sup>43</sup>

A recent study that investigated the effects of gelatin and HES 130/0.4 in a rat sepsis model found effects of both synthetic colloids on renal function and renal histology in comparison with crystalloid. Both synthetic colloids resulted in elevated levels of kidney-specific protein neutrophil gelatinase-associated lipocalin (NGAL) and significantly more histopathological kidney injury than crystalloid. Moreover, gelatin-treated animals showed significantly increased levels of creatinine and urea. The authors concluded that they had, to their knowledge, demonstrated for the first time that gelatin also impaired the kidney function.<sup>64</sup>

Gelatin adverse effects may have been masked when used as control for HES solutions.<sup>52</sup> Of note, measurements of renal function after gelatin were similar to HES 200/0.6 in patients undergoing aortic aneurysm surgery<sup>65</sup> and to HES 130/0.4 in cardiac surgery.<sup>66</sup>

Currently, dextrans are rarely used. In their study of dengue shock syndrome in children, Wills et al.<sup>6</sup> found that 8% of children receiving dextran had a severe febrile response likely due to bacterial contamination of fluid batches.

### Excess Mortality Associated with Higher Doses of HES?

High doses of HES may be associated with higher mortality in patients at risk. Septic patients showed a trend toward increased 90-day mortality if they received 10% HES 200/0.5 compared with modified RL (41.0% vs 33.9%,  $P = 0.09$ ). This excess mortality seemed to be driven by patients who received HES in higher cumulative doses. There was no difference between 90-day mortality rates in patients who received study fluids according to protocol (RL 33.6%,  $n = 256$ ; HES  $<22$  mL/kg, 30.9%,  $n = 162$ ,  $P = 0.56$ ; unpublished data). However, patients whose daily dose limits of HES were overstepped at least once also received HES in a cumulative dose of 136.0 mL/kg. Their 90-day mortality rate was considerably increased (57.6%) compared with patients without any dose violations who received a cumulative HES dose of 48.3 mL/kg (30.9%,  $P < 0.001$ ).<sup>5</sup>

It has been suggested that the high mortality rate was attributable to the fact that daily dose limits were exceeded at least once during the 21-day study period in the high-dose group. Although this may be true, it should be kept in mind that keeping to daily dose limits will not necessarily protect patients from adverse effects. For instance, renal failure with histopathological findings attributable to HES developed in a patient who received no more than 1 L of HES 130/0.4 along with  $>4$  L of crystalloids per day over 5

days.<sup>67,68</sup> HES side effects such as those that derive from tissue storage become apparent after high cumulative doses.<sup>69–71</sup> Unfortunately, as will be discussed below, safe cumulative doses are unknown.

A trend toward increased mortality in patients with severe sepsis receiving HES compared with patients receiving other fluids (crystalloids, albumin, dextran, or gelatin) was also reported in 2 recently published meta-analyses.<sup>14,15</sup>

Retrospective analysis of hospital discharge data of approximately 20,000 cardiac surgical patients showed that the risk of hospital mortality was decreased after administration of albumin compared with HES or dextran (OR, 0.80; 95% CI, 0.67–0.96).<sup>72</sup>

It is unclear how HES administration might impair survival, but tissue storage may have a role. Synthetic colloids are either broken down by serum amylase and excreted via the kidneys or temporarily absorbed into lysosomes of liver, kidney, lymph nodes, and other tissue. This phenomenon is dose dependent and may be increased in the presence of renal failure. In patients with impaired renal function, frequent plasma replacement with HES resulted in an increase in plasma chitotriosidase activity, which is a marker of activated foamy macrophages.<sup>70</sup> Massive colloidal tissue storage may have impaired ventilation and transport of bile acids and renal function in a patient with acute respiratory distress syndrome.<sup>69</sup>

### Is There a Safe Dose for HES?

There is no known dose threshold for synthetic colloids below which they may be safely administered to patients at risk. Daily dose limitations for HES are somewhat arbitrary because they were originally derived from dose limits for dextran that were considered tolerable in view of its coagulopathy effects but were not based on clinical studies.<sup>73</sup> When HES was introduced into clinical practice 4 decades ago, coagulation was the major concern but not tissue storage, which was considered to be negligible. There are no dose limitations for gelatin. All data point to the fact that adverse effects of HES and gelatin correlate with the overall administered, i.e., cumulative dose, rather than with doses administered per day. In the VISEP study, patients who never received doses of 10% HES 200/0.5 above the recommended daily limit of 20 mL/kg still had an increased incidence of renal failure compared with patients receiving RL (25.9% vs 17.3%,  $P = 0.035$ ). Rioux et al.<sup>54</sup> found that increasing doses of 10% HES 250/0.45 above 14 mL/kg was associated with the risk of AKI in 563 cardiac surgical patients but stated that they could not exclude absence of risk at doses below 14 mL/kg,<sup>54</sup> and persisting renal failure developed after a cumulative HES dose of 81 mL/kg over 5 days.<sup>67</sup> Higher cumulative doses in the range between 250 and 400 mL/kg were associated with extensive tissue infiltrates with foam cells, severe weight loss, organomegaly, ascites, and myelofibrosis<sup>70</sup> or thrombocytopenia, and liver failure.<sup>74</sup>

### (4) IS THE THIRD-GENERATION HES 130/0.4 SAFER THAN OLDER-GENERATION HES SOLUTIONS?

On one hand, 3 of 4 reports on HES 130/0.4 in ICU patients<sup>57,63,67,75</sup> suggest that the renal safety profile of this

compound may be similar to older starches. Two have been discussed above; the third is a multinational observation study with >1000 patients that found a similar incidence of renal failure after HES/130/0.4 and older starches (20/119, 16.8% vs 53/270, 19.6%,  $P = 0.51$ ).<sup>57</sup>

On the other hand, it has been suggested that third-generation HES 130/0.4 is safer than older HES preparations because of its different pharmacokinetic properties. A current Medline query for "HES 130/0.4" results in >140 citations, and a recent review cites numerous studies.<sup>17</sup> However, upon closer examination, these studies are not designed to answer the open questions about the safety of HES 130/0.4.

### Lack of Studies in Critical Care

A recent meta-analysis that screened published and unpublished clinical studies up to December 2008 to analyze renal outcomes in critically ill patients identified only 1 study on HES 130/0.4 that fulfilled the inclusion criteria, namely, an RCT in adults requiring acute volume therapy and admission to an ICU or emergency unit and comparing HES with non-HES fluids.<sup>14</sup> This study compared the effects of unspecified amounts of 6% HES 130 and albumin 20% on the pulmonary catheter wedge pressure in 20 patients; the observation period was 5 days.<sup>75</sup> The quality of this study was ranked as 2 by JADAD score, which ranges from 0 to 5 with 5 being the highest score.<sup>14</sup> A recent observational ICU study found the incidence of AKI to be similar in patients who received HES and in those who did not, but groups were imbalanced, sample sizes were small, and cumulative HES doses very low.<sup>76</sup>

Despite its lack of evidence in severely ill patients, HES 130/0.4 has been given to >24 million patients worldwide according to a manufacturer. In one-third of 73 Scandinavian ICUs that participated in a survey published in 2008, colloids were used as first-line fluid for resuscitation and HES 130/0.4 was the preferred colloid in the majority of ICUs.<sup>77</sup> A majority of responders to a questionnaire about intravascular volume replacement strategies in the operating room or the ICU in Switzerland consider HES to be the most effective substance to correct hypovolemia and believe that HES improves patient outcomes. Two-thirds of respondents reported switching to HES 130 from other infusion fluids during the last 5 years.<sup>78</sup> In the last years, a number of reviewers have strongly propagated the use of HES 130 in critically ill patients.<sup>17,79,80</sup> A Canadian survey shows that marketing may also determine practice habits. Physicians who used more pentastarch were more likely to have been visited by a drug detailer for HES than physicians who used less.<sup>81</sup>

### Poor Methodological Quality of Studies in the Perioperative Setting

Conclusions about the safety of HES 130/0.4 are mainly drawn from the perioperative setting.<sup>17</sup> However, most of these studies cannot contribute to the safety debate because of their unsuitable methodology, e.g., small sample size, short observation period, low cumulative dose of study fluid, and unsuitable control fluids. This is illustrated by the study data submitted to the Food and Drug Administration (FDA) for approval of HES 130/0.4 (Volumen®;

Fresenius Kabi, Bad Homburg, Germany) in the United States on behalf of the manufacturer.\*

The FDA study roster includes 21 studies with 1315 patients. Twelve studies were ranked as volume replacement studies ( $n = 705$ ), and the remaining were studies on sudden hearing loss ( $n = 397$ ), stroke ( $n = 146$ ), or uncontrolled phase I studies ( $n = 67$ ). Nine volume replacement studies were available in the literature for closer scrutiny ( $n = 523$ ).<sup>82–90</sup> One study was an exploratory high-dose study of hypervolemic hemodilution in severe head injury ( $n = 31$ ).<sup>90</sup> The remaining 8 studies were surgical studies in cardiac, major vascular, orthopedic, or urological surgery. The median patient number was 59.5 patients (interquartile range [IQR], 43–90 patients), median study duration until achievement of primary end point was 20 hours (IQR, 5–42 hours), and median duration of the study for secondary or exploratory outcomes was 1.00 day (IQR, 1.00–4.75 days). In the control groups, 62.7% of patients received 6% HES 200/0.5; the others received 6% HES 650/0.7 (19.6%) or 3% gelatin (11.9%), all fluids that have known renal and hemostatic side effects.

According to their primary end points, 5 studies were designed to show equivalence of needed colloid volumes or achieved hemodynamic variables, and 2 were exploratory. No conclusion about safety outcomes can be drawn from these studies with low sample size. The only study to explore a safety outcome compared peak increases in serum creatinine after abdominal aortic surgery in patients with creatinine clearance <80 mL/min. No difference was found between 6% HES 130/0.4 and 3% gelatin.<sup>85</sup>

Acknowledging the meager database on patients at risk, the FDA committed the manufacturer to perform postmarketing studies in patients with severe sepsis including subjects with renal dysfunction and at risk for deterioration of renal dysfunction and in children 2 to 12 years.<sup>†</sup>

Only a few studies in the perioperative setting have chosen primary end points with regard to the safety issue. In patients with cardiac surgery, 2 studies with 40 to 50 patients intending to detect differences in creatinine clearance 24 hours after surgery found no difference between HES 130/0.4 and 4% gelatin or 5% albumin,<sup>91,92</sup> whereas 1 study ( $n = 60$ ) found a significantly lower creatinine clearance in the gelatin group.<sup>66</sup> Mahmood et al.<sup>65</sup> observed the urinary  $\alpha_1$ -microglobulin/creatinine ratio in 62 patients in abdominal aortic surgery and found no difference between HES 130/0.4 and HES 200/0.6, but higher ratios in the gelatin group.

Kasper et al.<sup>93</sup> investigated chest tube drainage at 24 hours after cardiac surgery in 120 patients; the authors found no difference compared with 6% HES 200/0.5. Similarly, Van der Linden et al.<sup>94</sup> calculated net red blood cell loss in 132 cardiac surgical patients but found no difference compared with 3% gelatin.

Outcomes from other recent studies performed in the surgical setting that were designed to detect differences of

\*FDA (2007). NDA Review Memo (Mid-Cycle). Available at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/NewDrugApplicationsNDAs/UCM083393.pdf>. Accessed November 13, 2009

†FDA (2008). Corrected Approval Letter. Available at: <http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/NewDrugApplicationsNDAs/ucm083135.htm>. Accessed November 13, 2009

clinically irrelevant surrogate markers such as interleukin-6 secretion<sup>34,38,95</sup> or muscular tissue oxygen tension<sup>35</sup> do not contribute to the safety debate.

In contrast, a comparison of pooled data on blood loss comparing HES 130/0.4 with HES 200/0.5<sup>96</sup> found a small, but statistically significant difference in favor of HES 130/0.4 in the overall population. Data were derived from 7 studies that were mainly explorative or designed to show immediate volume effects. The only larger study in 120 cardiac surgical patients, which was powered to detect differences in chest tube drainage (see above), found no difference between groups.<sup>93</sup> Accordingly, in the pooled analysis, HES 130/0.4 led to similar blood loss as HES 200/0.5 in the overall group of cardio-surgical patients.<sup>96</sup>

Likewise, a European multicenter observational study, which found that HES is not associated with increased RRT, is also not suitable to estimate the safety of this compound. HES solutions were not specified and cumulative dosage over a study period of 14 days was only 15 mL/kg.<sup>97</sup>

Studies on renal outcomes also lack sensitive end points such as the RIFLE criteria, which allow a refined and graded assessment of acute renal injury.<sup>98</sup> In January 2010, a Cochrane meta-analysis was published on the use of HES for the treatment of vascular depletion and its effects on renal outcomes.<sup>13</sup> The authors performed a predefined pairwise comparison between high-MW and low-MW starches. The systematic search of the literature only revealed 5 studies in which HES 130/0.4 was compared with older HES solutions with data on RRT or "RIFLE" criteria. The authors concluded that "there is insufficient evidence to assess differences between HES products with respect to clinical kidney outcomes. More specifically, there is insufficient clinical evidence to suggest that 6%130/0.4's favorable pharmacokinetics compared to older HES products result in improved kidney outcomes."<sup>13</sup>

It is possible that side effects of different HES solutions may differ by degree; however, the overall safety of each new solution should first be assessed clinically compared with an equally effective but considerably safer solution such as crystalloid. HES safety studies should be large-scale studies in patients at risk with acute need for volume therapy, with clinically relevant end points, and with long enough study periods to detect differences in long-term mortality and morbidity. Of note, the increased mortality rate in patients who received higher cumulative doses of HES 200/0.5 only started to become apparent after 20 days in the VISEP study. This latency period in critically ill patients may be attributable to storage of HES in organs of the immune system, in a similar manner as itching, which is due to HES storage in cutaneous nerves, typically manifests late, between 1 and 6 weeks after administration.<sup>58</sup> Crystalloids in general and albumin in many conditions except in patients with closed head injury (SAFE) have been shown to be safer than older starches in critically ill patients. They should therefore be considered the gold standard for future safety trials. It is for this good reason that listed ongoing or planned major RCTs and multicenter studies use crystalloids as control fluids: (1) CHEST study (ANZICS): HES 130/0.4 vs 0.9% NaCl in critically ill patients (planned enrollment  $n = 7000$ , NCT00935168), (2)

Scandinavian Starch for Severe Sepsis/Septic Shock Trial: HES 130/0.4 vs Ringer acetate solution in severe sepsis patients (planned enrollment  $n = 800$ , NCT00962156), and (3) University of Manitoba: HES 130/0.4 versus RL to assess blood loss in cardiac surgery (planned enrollment  $n = 500$ , NCT00801190).

After the results of these studies are analyzed, we should know if HES 130/0.4 is safer than older HES solutions in critically ill patients.

## CONCLUSION

The preferred use of colloidal solutions for resuscitation of patients requiring intravascular volume replacement is based on rationales that are not supported by clinical evidence. Data not only from meta-analyses but also from recent large-scale clinical trials show that resuscitation with colloids is not more effective than crystalloids in critically ill patients. Colloid effects on intravascular volume are only marginally different from crystalloid effects and, more importantly, are transitory and without effect on long-term clinical outcomes.

Overall cumulative crystalloid volumes do not much exceed cumulative colloid volumes to achieve the same predefined end points; adequate resuscitation is achieved by 1- to 2-fold of total crystalloid relative to total colloid volume. Crystalloid/colloid volume ratios quoted in textbooks to the extent of 1 to 4 need to be reconsidered.

Because there is no clinically relevant benefit to the administration of synthetic colloids, safety is an important consideration. If there is no measurable benefit, why should harmful effects be risked? HES-associated side effects in critically ill patients are coagulopathy, renal failure, and tissue storage. These effects are dose related. New data indicate that mortality rates may be increased after high cumulative doses. However, no cumulative dose limits exist and a safe threshold needs to be determined in studies of high-risk patients and with observation periods of 90 days. Such studies on HES 130/0.4 are still missing despite its widespread and increasing use. These concerns also relate to gelatins.

Many clinicians believe that a resuscitation strategy based only on crystalloids may be untested. However, it should be emphasized that the SAFE study with nearly 7000 patients, the VISEP study with >500 patients with sepsis, as well as the Wills study in >120 children with dengue fever have demonstrated that it is feasible and safe to resuscitate only with crystalloids.<sup>4-6</sup>

In summary, synthetic colloids are without superior effect in critically ill adults and children but must be considered harmful depending on the cumulative dose administered. Because there are safer and equally effective alternatives in the form of crystalloids, we question the use of synthetic colloids outside the context of clinical studies. Those who believe that the evidence is insufficient to ban the use of synthetic colloids should consider that the adverse effects are dose dependent and are more pronounced in patients with preexisting renal dysfunction. ■■

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