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SPECIAL ARTICLE

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CONTRA: Hydroxyethyl starch solutions are unsafe in critically ill patients

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Abstract *Purpose:* To describe the risk–benefit profile of hydroxyethyl starch (HES).
Methods: Narrative review.
Results: (1) Efficacy: no single clinical study or systemic review has shown that administration of any HES solution confers a clinically relevant benefit compared to crystalloids in critically ill patients or surgical patients in need of volume replacement. Contrary to beliefs expecting a ratio of 4:1 or more for crystalloid to colloid volume need, recent studies of goal-directed resuscitation observed much lower ratios of between 1 and 1.6. (2) Safety: HES administration is associated with coagulopathy, nephrotoxicity, pruritus and increased long-term mortality. Clinical studies claiming that modern HES 130/0.4 is safe have serious methodological drawbacks and do not adequately address the safety concerns. *Conclusions:* Given the complete lack of superiority in clinical utility studies and the wide spectrum of severe side effects, the use of HES in the ICU should be stopped. The belief that four times as much crystalloid as colloid fluid volume is needed for successful resuscitation is being seriously questioned.

Keywords Colloids · Crystalloids · Hydroxyethyl starch · Efficacy · Safety · Critically ill

Introduction

Issues of safety need to be discussed in the context of efficacy. This is especially true for the question of hydroxyethyl starch (HES) safety, where presumed benefits are considered to outweigh potential harm. Colloids in general and starches in particular are known to be more effective plasma expanders in the short term than crystalloids because they can stabilize hemodynamic parameters faster. However, cardiovascular parameters are surrogate markers for the long-term clinical benefit that one hopes to achieve, and scrutiny of clinical evidence is still necessary to support or disprove the claims of superiority of crystalloids over starches in the critically ill.

Well-designed outcome studies in the ICU are scarce. Meta-analyses consistently confirm that colloids are not superior to crystalloids in these patients [1]. In line with systematic reviews, recent data from large clinical studies in various populations of critically ill patients show that colloid resuscitation provides no clinically relevant outcome benefit [2–4]. Against this background, it is a concern that HES administration is associated with dose-related side effects that are not trivial, such as coagulopathy [5], nephrotoxicity [4, 6, 7], protracted severe pruritus [8] and even an indication for increased long-term mortality and morbidity [4, 9, 10].

We argue that HES should be avoided in critically ill patients, because the evidence for its unsafety in these patients is stronger than the evidence for its clinical benefits. More generally, the common belief in the superiority of colloids over crystalloids in the resuscitation of the critically ill is being questioned.

Methods

A literature search of published data in MEDLINE was undertaken. Additional resources were reference citations from published randomized trials or systematic reviews as well as material available on the FDA website in context with the recent approval of HES 130/0.4 [11]. We evaluated outcomes in randomized clinical trials, with focus on sample size and study design, clinically relevant endpoints, type of HES, comparator fluid, cumulative doses, observation periods, and patient inclusion and exclusion criteria.

Results

Efficacy

Our search strategy brought up only six clinical trials that fulfilled our criteria of clinically relevant endpoints, adequate sample size for the selected endpoints and suitable non-colloid comparator fluids. Only two of them were conducted in critically ill patients [2, 4]. In the first study of 383 children with Dengue shock syndrome, resuscitation was equally successful with either Ringer's lactate, 6% dextran 70 or 6% HES 200/0.5 ($p = 0.65$) [2]. In the other multicenter ICU study of 537 adult patients with severe sepsis resuscitated with either Ringer's or 10% HES 200/0.5, the pre-specified endpoints 28-day mortality rate and mean SOFA score were similar between groups ($p = 0.48$ and $p = 0.16$, respectively) [4].

The other identified studies dealt with hemodilution therapy in ischemic stroke [12, 13], sudden sensorineural hearing loss [14] and hypertensive disorders of pregnancy [15]; none of these found superiority of modern HES solutions (HES 200/0.5 or HES 130/0.4) over non-colloid comparators, including Ringer's, saline or 5% glucose fluid.

It is generally believed that three to four times more crystalloid than colloid volume is needed to achieve an equivalent plasma volume expansion [16, 17]. However, the authors of a recent meta-analysis raised serious doubt about this belief. They pointed out that in the SAFE trial [3], in which fluid administration was blinded, the ratio of albumin to saline was 1:1.4 and thus much less than expected [1]. Results from several more recent studies support this finding. In the other major ICU fluid therapy study of the last years that compared colloids with crystalloids, the crystalloid/colloid volume ratio was in the range of 1.6 on day 1 and 1.4 over the first 4 days [4]. In a cardiovascular surgical setting, perioperative fluid loading with saline, gelatin, HES or albumin to achieve target central venous or pulmonary capillary wedge pressures showed that crystalloid/colloid volume ratios were in the range of 1 to 1.3 [18]. In children with Dengue shock syndrome, effective resuscitation was achieved with the same amount of crystalloids or colloids within the first 2 h [2]. One reason for this may be that in conditions with vascular leakage, colloids quickly leave the intravascular space and pull fluids with them. In this study comparing HES 200/0.5 or dextran with Ringer's, both colloids led to a rebound increase in hematocrit between 2 and 6 h with a median increase of 5% (90% range, −8 to 20%) for dextran and 5% (90% range, −10 to 21%) for starch as compared with 0% (90% range, −12 to 12%) for Ringer's lactate ($p < 0.001$) [2].

Safety

Coagulation

HES administration reduces circulating factor VIII and von Willebrand factor levels and leads to impairment of platelet function, prolongation of partial thromboplastin time and activated partial thromboplastin time with the subsequent risk of bleeding complications [19]. In cardiac surgery, large-scale trials have revealed significant increases in postoperative blood loss and blood product use in patients receiving HES as priming solution or fluid therapy [5, 20]. HES 450/0.7 was a risk factor for hemorrhage also in doses less than the recommended maximum. The incidence of postoperative bleeding increased similarly in patients who received HES 470/0.5 or HES 200/0.5 as compared to albumin [5]. HES also led to severe cerebral bleeding in patients with subarachnoid hemorrhage [21] and acute ischemic stroke [12]. In septic patients with sepsis, patients receiving 10% HES 200/0.5 required more units of red packed blood cells ($p < 0.001$) than patients receiving Ringer's [4].

Renal function

HES 200/0.62 administration to kidney donors was associated with increased rates of delayed graft function (DGF) in recipients [22, 23]. By retrospective analysis, exposure to >1,500 ml HES was an independent risk factor for DGF in patients with kidney transplants [24]. In liver transplant patients, chronic nephrotoxicity with osmotic nephrotic lesions and secondary renal failure was described as long as 10 years after administration of HES 200/0.62 [7]. A recent European observational study on 3,147 critically ill patients in 198 intensive care units concluded that HES had no influence on the incidence of renal failure, but the reported cumulative dose of HES less than 15 ml/kg; HES recipients at baseline had less exposure to renal replacement therapy (2.2%) than patients not exposed to HES (4.4%, $p < 0.001$), and actual exposure to HES during the ICU stay was associated with an increased requirement for renal replacement therapy (10.6 vs. 9.3%; $p = 0.006$), an effect

that did not persist in a multivariate analysis of results from a subset of patients [25]. Two large-sampled prospective clinical studies have now provided evidence for HES nephrotoxicity in critically ill patients. In 129 patients with sepsis, 6% HES 200/0.62 led to a higher frequency of acute renal failure (ARF) than 3% gelatin ($p = 0.028$), and the use of HES was an independent risk factor for ARF [OR 2.57 (1.13–5.83), $p = 0.026$] [6]. In 537 patients with severe sepsis, resuscitation with 10% HES 200/0.5 compared to modified Ringer's lactate significantly increased ARF ($p = 0.002$) and days on renal replacement therapy in a dose-related manner [4]. Notably, manufacturer's contraindications for the use of 10% HES 200/0.5 were followed, and creatinine values at inclusion were comparable with other studies [6, 26]. Non-study colloids were given to a quarter of patients, but they were equally distributed among groups and patients received only small and comparable amounts (500 ml median dose over 21 days, $p = 0.38$). ARF and need for renal replacement therapy (RRT) also occurred significantly more often in patients who received HES in doses never exceeding the recommended daily maximum ($N = 419$, ARF: 30.0% in the HES arm vs. 22.1% in the crystalloid arm, $p = 0.044$; RRT: 25.9 vs. 17.3%, $p = 0.035$). The median cumulative dose of HES in these patients was 48.3 ml/kg, which corresponds to approximately 4 l of HES solution in an 80-kg patient [4].

Tissue storage and long-term outcome

HES is taken up by lysosomes and stored in almost all tissues, including the reticuloendothelial system. These adverse effects depend on cumulative dose and susceptibility of the patient and may become apparent only after longer observation periods [4].

After chronic administration, HES is also stored in macrophages, bone marrow and liver cells with the aspects of a storage disease, such as foamy macrophage syndrome, acquired lysosomal storage disease, hydrops lysosomalis generalisatus and worsening of liver disease with ascites [10, 27–29]. In septic patients, higher doses of 10% HES 200/0.5 were associated with a higher 90-day mortality compared to Ringer's (57.6 vs. 30.9%, $p < 0.001$). The cumulative dose of HES (not of Ringer's lactate) was directly associated with the rate of death at 90 days [4]. Poorer survival was also linked with HES or dextran administration compared to albumin in an analysis of hospital discharge data of 19,578 cardiac surgery patients [9]. In patients undergoing cardiopulmonary bypass surgery, evidence based perfusion care changes that included elimination of HES were associated with a 67% decrease in the relative odds of death [30]. In 160 patients with subarachnoid hemorrhage, colloid fluids (HES 200/0.5 or gelatin) increased the risk of unfavorable neurological outcome at 6 months ($p = 0.035$), while administration of crystalloids reduced the risk ($p = 0.005$) [31]. In hypertensive disorders of pregnancy, administration of HES 200/0.5 led to an increase in the rate of caesarean sections and a trend toward shortened pregnancies and need for oxygen in neonates in the HES group [15]. It is known that HES is taken up in the placenta in these patients [32].

Pruritus is a dose-related adverse effect with late onset that can be severe [8]. Accumulation of HES in cutaneous nerves was found to be responsible for the protracted itching [33].

Safety of "new" HES 130/0.4

There are claims that the latest HES solution (HES 130/0.4) is safe in regard to coagulation and renal adverse effects. However, adverse effects may be an inherent side effect of the compound, and there are indications that the latest HES 130/0.4 may not be an exception to the rule. In patients with severe head injury who received HES 130/0.4 and HES 200/0.5 in high cumulative doses, cerebrovascular bleeding events were similar in both groups [34]. In cardiac surgical patients, HES 130/0.4 and HES 200/0.5 at maximum daily doses were associated with similar incidences of postoperative bleeding [35]. A recent pooled analysis derived that post-surgical blood loss is significantly less after HES 130/0.4 than after HES 200/0.5. However, the derived effects are marginal, and in the largest group of cardiac surgery patients, there was no difference in estimated blood loss, calculated red blood cell (RBC) loss, or transfusion of RBC, platelets or fresh frozen plasma [36].

HES 130/0.4 also raised sensitive markers of renal impairment [37] and led to a progressive increase of plasma accumulation in relation to pre-existing renal impairment [38]. In a retrospective, matched pair analysis of kidney transplants, HES 130/0.4 administration was associated with a similar incidence of delayed graft function as HES 200/0.62 [39].

In rats, HES 130/0.4 also led to long-term storage in organs and carcass, although in several-fold less amounts than HES 200/0.5. However, accumulation in the kidney occurred in similar amounts [40]. HES 130/0.4 is also associated with pruritus in healthy volunteers with a duration of 8–16 days [41] and with more frequent and longer lasting itching than HES 200/0.5 after hemodilution therapy for sudden hearing loss [11].

Claims that new HES 130/0.4 is devoid of severe side effects are based on clinical studies that have severe limitations on closer scrutiny. Our literature search yielded 26 clinical studies with HES 130/0.4 administration in surgery or sepsis. These were mostly volume efficacy studies with clinically irrelevant endpoints such as volume need, ex-vivo clotting parameters, postoperative creatinine clearance or interleukin-6 response. Twenty-two studies reported observation periods of 48 h or less. Nineteen studies used unsuitable comparators such as

other HES solutions or gelatin. Only seven studies compared HES to albumin or crystalloid [42–48] with a mean of 39.3 study patients and a mean study period of 1.4 days. Six of these reported cumulative doses with a mean of 44.2 ml/kg, which is less than the recommended maximum dose for 1 day (50 ml/kg). Similar limitations also apply to the clinical studies that provided the data for approval of HES 130/0.4 in the US [11]. Data are derived from 21 mainly non-inferiority studies in low risk patients or volunteers with a mean study period of 2 days, mean cumulative dose of 41.9 ml/kg, and mostly other HES and gelatin as comparator fluids. There is no evidence on the safety of HES 130/0.4 in severe sepsis or intensive care patients with pre-existing renal impairment or risk for renal dysfunction. Hence, none of these studies are able to dispel concern about the safety of HES in critically ill patients.

Conclusion

To date, no single study or meta-analysis was able to show that the use of any HES solution confers an outcome benefit in critically ill patients. On the other hand, several large-scale trials show that the use of HES in these patients is associated with serious adverse effects. These adverse effects are dose-related and include coagulopathy, nephrotoxicity and long-term tissue storage, which can seriously impair long-term morbidity and mortality. Claims that the new HES 130/0.4 is safe derive from small studies with serious methodological drawbacks, such as unsuitable comparators, too short observation periods, low cumulative dose and low-risk patients. Moreover, recent studies in surgical and critically ill patients suggest that the crystalloid/colloid ratio needed for successful fluid resuscitation is much less than previously believed.

Given their spectrum of severe side effects and their complete lack of superiority in clinical utility studies, the use of starches in the ICU should be stopped for safety reasons.

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Conflict of interest statement The authors report no current conflict of interest.

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