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EDITORIAL

# Is the literature inconclusive about the harm from HES? No

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## Introduction

Colloid solutions may be more effective than crystalloid solutions in expanding the intravascular space, which may result in improved hemodynamics and reduced tissue edema. Whether this is clinically important is unknown. Despite lack of evidence of overall benefit in terms of clinical or patient-important outcome measures, hydroxyethyl starch (HES), an artificial colloid solution, has been used in a variety of clinical settings to treat hypovolemia including during surgery, after trauma and burns, in sepsis, and in critically ill patients. As we will outline below, HES has clear side effects based on well-described pathophysiologic pathways resulting in worse outcome in critically ill patients.

## Acute kidney injury

Hydroxyethyl starch has been shown to increase the risk of acute kidney injury (AKI) and need for renal replacement therapy (RRT) as compared to other fluid solutions in different clinical settings [1]. The effects are independent of molecular weight, molar substitution, C2/C6 ratio, and dose of HES. Increased use of RRT with HES vs other fluids has been shown in surgical and non-surgical intensive care patients, and in patients with sepsis [2–5]. Because most of these data are from trials done in ICU, the effects of HES on kidney function in the intraoperative period have yet to be settled.

The nephrotoxic pathway of HES is likely secondary to renal tissue uptake and storage because HES cannot be degraded once it leaves the circulation [6, 7]. Moreover, HES is by no means confined to the intravascular compartment. Up to 50 % of administered volumes cannot be accounted for in blood or urine at 24 h after infusion meaning that this amount resides in other compartments where it cannot be degraded [6]. In the kidney, HES may induce osmotic nephrotic lesions [7] and tubular obstruction by hyperviscous urine and inflammation [8]. HES-related inflammation has also been observed in other organs months after intravenous infusion, including liver and bone marrow [7].

## Bleeding

In general, the data on HES and clinical bleeding are less robust than those on AKI. However, recent trials have shown increased risk of bleeding with the use of HES as compared to crystalloid solutions in patients with sepsis [9] and those undergoing major surgery [10, 11]. In a meta-analysis of patients undergoing cardiac surgery, HES solutions were associated with increased postoperative blood loss and rates of reoperation for bleeding compared to albumin [12]. Other meta-analyses including data on HES and bleeding have been published by authors with ties to the industry [13]. Their results have favored HES, but the authors have been criticized for biased inclusion of control groups and data imputation. HES-induced bleeding is likely the result of direct effects on hemostasis through impaired fibrinogen/fibrin polymerization resulting in weaker and smaller blood clots [14].

## Increased risk of death

After inclusion of data from large high-quality trials [2, 15], the updated Cochrane meta-analysis of colloids vs crystalloids in critically ill patients showed increased mortality with HES [16]. Additional meta-analyses confirmed this finding using different methodologies and in different settings underlining the robustness of the data [3, 17].

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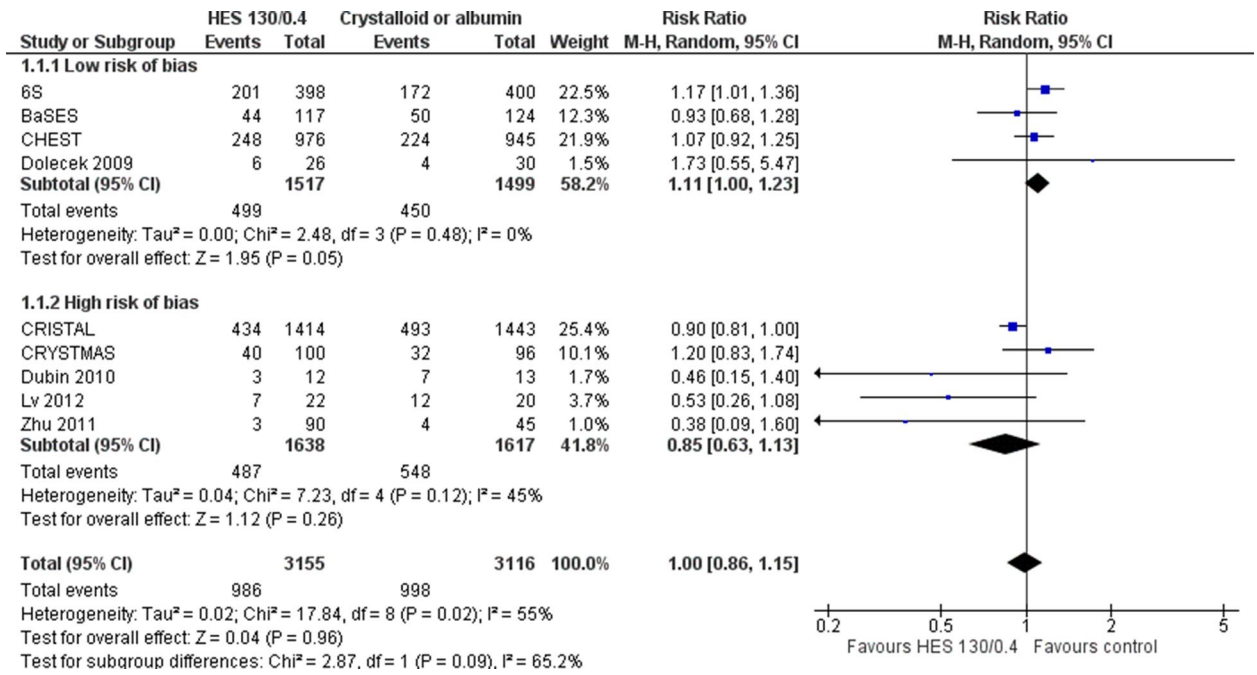


**Fig. 1** Forest plot of all-cause mortality in relation to risk of bias in randomized trials of HES vs crystalloid/albumin solutions in patients with sepsis. We thank Dr N. Haase for updating the plot published in the 2013 meta-analysis [3] with data from the CRISTAL trial. The trials were categorized according to overall risk of bias using the Cochrane criteria (www.cochranehandbook.org). Using these criteria, risk of bias in one or more domains categorizes a trial as high risk of bias. Conversely, for a trial to be categorized 'low risk of bias' it cannot have evidence of bias in any of the domains. The CRISTAL trial had risk of bias in 3 of 8 domains (uncertain allocation concealment, lack of blinding, and baseline imbalance) and was therefore categorized as having high risk of bias. The CRYSTMAS trial appeared to have no risk of bias in the methodological domains, but outcome reporting may have been selective [20]. It was sponsored by Fresenius Kabi (vested financial interests) and the main author had previously published papers with conclusions favoring HES (academic bias). The CRYSTMAS trial was, therefore, categorized as having high risk of bias. *Size of squares* for risk ratio reflects weight of trial in the pooled analyses. *Horizontal bars* represent 95 % confidence intervals

## Misleading trial results

Risk of bias is very important when interpreting trials of HES. When adding mortality data from the subgroup of patients with sepsis in the CRISTAL trial (even though not strictly randomizing patients to HES vs crystalloid [18]) to the cumulative evidence of HES vs crystalloid/albumin in sepsis [3], there was heterogeneity in the results for mortality based on risk of bias; the high risk of bias trials showed the opposite of the low risk of bias trials (for details, see Fig. 1). It is well established that risk of bias results in overestimation of the intervention effect on objective outcome measures in RCTs [19], and this appears also to be the case for the effect of HES vs crystalloid/albumin on mortality. The overall result of this meta-analysis (Fig. 1) is heavily affected by the high risk of bias trials, which also shows how misleading these analyses may be if proper risk of bias adjustments are not made.

## Conclusions

The evidence from high-quality meta-analyses shows that fluid therapy with HES vs crystalloids increases the rate of AKI and mortality in critically ill patients. Thus, the European Medicines Agency (EMA) has made the legally binding decision (EMA/809470/2013) that HES cannot be used in these patients nor in those with sepsis or burn-related injury. Although currently data are insufficient to identify a difference in outcomes of perioperative fluid therapy in non-cardiac surgery, the use of HES also appears to be associated with increased risk of bleeding in patients with sepsis and those undergoing surgery as compared with the use of crystalloid or albumin solutions.

The literature about harm of HES is conclusive and the mechanisms of toxicity have been identified. The harmful effects of HES appear to be common to all HES classes and dose dependent. No safe dose of HES has been defined [1, 17]. Since there are no data from trials with adequate methodology and power showing clinically important benefits from using HES in any clinical setting, the EMA has requested the marketing authorization holders of HES-containing medicinal products to perform postauthorization safety studies. Results of these studies will determine if the use of HES will have to be further restricted.

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