Should hydroxyethyl starch be banned?

In their Correspondence in The Lancet, Ian Roberts and colleagues (Feb 12, p 736) ask the director general of WHO to ban the use of hydroxyethyl starch (HES) solutions worldwide “to protect patients”. Several clarifications and corrections are needed to place the authors’ arguments into proper perspective.

Roberts and colleagues’ state that evidence from high-quality trials in kidney donors and in patients who are critically ill and septic has shown that the use of HES is associated with serious adverse effects without benefits. They reference the study by Myburgh and colleagues1 in support of this statement. With respect to the claim that the trial was high quality, numerous aspects of Myburgh and colleagues’ study have been repeatedly criticised (including changes in the methods, statistical analysis, and data after publication, and questionable data interpretation), which resulted in a call to the authors to open the trial data for independent reanalysis.1,4 The authors refused to do so. Of note, the first three authors of this trial are co-authors of the Correspondence.1

With respect to the claim that HES causes adverse effects, in Myburgh and colleagues’ trial, significantly more patients in the saline group met risk, injury, failure, loss, and end-stage kidney injury (RIFLE) criteria for kidney dysfunction than did those in the HES group (57.3% vs 54.0%; p=0.007). Likewise, RIFLE-defined renal injury occurred significantly more often in the saline group than in the HES group (38.0% vs 34.6%; p=0.005). No significant difference was seen between the groups in the occurrence of RIFLE-defined renal failure (9.2% vs 10.4%; p=0.12).

Careful interpretation of existing data is needed. A systematic review of studies comparing the effects of HES on renal function with other fluids showed that in patients who were non-septic, HES was not associated with an increased incidence of renal replacement therapy (risk ratio 1.25, 95% CI 0.96–1.61), renal failure (1.32, 1.15–1.53), or RIFLE-defined renal failure (1.04, 0.86–1.27). HES was even associated with a lower incidence of RIFLE-defined renal injury or worse (ie, loss of renal function or end-stage renal disease) than were other fluids (0.85, 0.78–0.92).1 That the effects of HES differ with the underlying medical condition and the indication for its use is to be expected.

Roberts and colleagues2 state that during the WOMAN trial3 they became aware that many women with postpartum haemorrhage received colloids and, most often, HES. In that trial, 5714 (28.5%) of 20 060 patients had an estimated blood loss of 1–1.5 L, 3926 (19.6%) had an estimated blood loss of more than 1.5 L, and 3839 (19.1%) had a systolic blood pressure of less than 90 mm Hg. For most physicians working in acute or perioperative care, these complications are a clear indication for administration of colloids. Because albumin, gelatine, and dextran are either not available or considered inappropriate in many countries, the use of HES under such circumstances is to be expected. That HES contributed to the haemodynamic stabilisation of numerous women in acute severe haemorrhagic hypotension is quite possible. Furthermore, the use of HES in such settings is entirely in agreement with the 2013 European Medicines Agency (EMA) recommendations, which state that “HES solutions should only be used for treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient”.7

Roberts and colleagues8 state that WHO guidelines recommend the use of crystalloids in preference to colloids for the resuscitation of women with postpartum haemorrhage. However, the 2017 WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage, which the authors cite, states that “standard care in the context of this recommendation includes routine care for PPH [postpartum haemorrhage] treatment, including fluid replacement”.9 The types of fluids are not specified. Only the 2012 WHO guideline recommended the use of intravenous fluid replacement with isotonic crystalloids in preference to colloids, including the clarification that this recommendation was based on low-quality evidence.

Upon request from the Pharmacovigilance Risk Assessment Committee (PRAC), the EMA convened an ad-hoc expert meeting in London on Dec 18, 2017. After hearing and evaluating the views of the PRAC rapporteur and co-rapporteur, and of the marketing authorisation holders, the experts recommended that PRAC do not completely suspend HES solutions. They concluded that HES-containing solutions have a place under certain conditions, especially in patients with hypovolaemia caused by acute bleeding. The experts expressed concerns regarding potential alternative colloid solutions (eg, albumins, dextrans, and gelatines) because of their limited use and the absence of comparative data. The experts strongly recommended that HES-containing solutions should not be suspended before the results of the multicentre PHOENICS (NCT03278548) and TETHYS (NCT03338218) trials become available. Both are prospective, randomised, controlled, double-blind, parallel-group, multinational phase 4 trials done under the auspices of the European Society of Anaesthesiology. The trials will provide clinically relevant information regarding the safety and efficacy of a 6% HES solution (molecular weight 130 kDa) versus a balanced crystalloid solution in patients undergoing major elective abdominal surgery (PHOENICS) or in trauma patients (TETHYS). Of note, the EMA itself requested such clinical trials in surgical and trauma patients after the use of HES-containing solutions had been restricted in 2013. Importantly, only one of the seven experts opposed the use of HES. For unknown reasons.
Correspondence

none of the experts’ recommendations and suggestions are mentioned in the PRAC decision. Furthermore, although the PRAC recommendation is easily accessible on the EMA website, the minutes of the ad-hoc expert group meeting are not. Members of the EMA expert group reiterated the plea to make the CHEST data available for independent reanalysis.

Publications continue to document the absence of increased risk and even the improved outcomes associated with the use of HES under defined clinical circumstances. I entirely agree with the experts’ view that complete suspension of HES is not only unfounded by existing evidence, but would be hazardous to patients.

I report lecture honoraria from Fresenius Kabi Company; outside the submitted work.

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11 Kammerer T, Brettner F, Hilsenkopf S, et al. No differences in renal function between balanced 6% hydroxyethyl starch (130/0.4) and 5% albumin for volume replacement therapy in patients undergoing cystectomy: a randomized controlled trial. Anesthesiology 2018; 128: 67-78.

Roberts and colleagues’ Correspondence in The Lancet asking WHO to support a ban on the use of hydroxyethyl starch (HES) deserves clarification. First, registration of HES is not yet suspended; a legally binding decision by the European Commission is still pending. Second, Roberts and colleagues claim that HES was used to treat postpartum haemorrhage in the WOMAN trial. In fact, the publication doesn’t provide any information about HES treatment or its related adverse events. Third, the authors refer to their own studies as examples of high-quality trials, but these have been publicly criticised for methodological deficiencies and severe limitations. Notably, several inconsistencies have prompted medical societies and journals to ask for open access of CHEST data, ultimately without success. The so-called independent reanalysis of this study was published by the original authors themselves. 19 European national anaesthesiological societies expressed their surprise and disagreement when the European Medicines Agency (EMA) rushed the far-reaching recommendation to suspend the registration of HES on such a questionable basis. The EMA ignored increasing evidence indicating that such measures may have a positive impact on patients’ outcomes, and actively decided against waiting for the results of two large randomised controlled trials (initiated by EMA themselves) investigating the safety and efficacy of HES in the context of surgery and trauma (NCT03338218 and NCT03278548).

Speculation from Roberts and colleagues that manufacturers of HES might be putting vulnerable patients in low-income countries at risk in the future distracts from the real major global health issue: clinical decisions in Europe are no longer based on data and scientific debate but on majority decisions made by authorities.

DC has received lecture honoraria and research grants from B Braun, Fresenius Kabi, and Grifols. MJ has received lecture honoraria and research grants from Baxter, B Braun, CSL Behring, Fresenius Kabi, Grifols, and Serenumwerke. MJ is a member of the albumin advisory board of Grifols.

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