CRITICAL CARE

LETTER

Patient-centered outcomes and trials of hydroxyethyl starch

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Meybohm and colleagues [1] propose that hydroxyethyl starch (HES) may be used safely in hypovolemic patients by applying a clinical algorithm and by restricting the dose administered.

The authors question the validity of the results of the two trials that constitute over 60% of current data [2,3] and misleadingly state that in the Crystalloid vs. Hydroxyethyl Starch Trial (CHEST), HES administration did not increase the use of renal replacement therapy by referring to the adjusted analyses that were published in the electronic supplement [2]. The unadjusted analysis was pre-specified as the principal outcome measure and is the appropriate measure to influence clinical practice. The authors also ignore the consistent signal of harm associated with HES, specifically increased mortality and use of renal replacement therapy that is evident despite wide variations in aggregate doses of HES in the three major clinical trials: 70 ml/kg in the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis trial [4], 44 ml/kg in the Scandinavian Starch for Severe Sepsis/Septic Shock study [3], and 5 ml/kg in CHEST. Meybohm and colleagues make no comment that adverse effects of HES represent an overall toxic effect caused by increased tissue accumulation that is recognised as a dose-dependent, generic HES effect [5].

The 'presumably correct indication' and the algorithm they propose have not been validated nor are they supported by any credible clinical evidence. Their proposed algorithm and target population must be evaluated in rigorously conducted randomized controlled trials before being considered for adoption into clinical practice. Given the consistent evidence that HES is nephrotoxic and may increase mortality [6], it is doubtful that institutional ethics committees would approve such a trial, or that informed patients would consent to participate.

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Abbreviations
CHEST: Crystalloid vs. Hydroxyethyl Starch Trial; HES: Hydroxyethyl starch.

Competing interests
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References

1. Meybohm P, Van Aken H, De Gasperi A, De Hert S, Della Rocca G, Girbes AR, Gombotz H, Guidet B, Hasibeder W, Hollmann MW, Ince C, Jacob M, Kranke P, Kozek-Langenecker S, Loer SA, Martin CD, Siegemund M, Wunder C, Zacharowski K: **Re-evaluating currently available data and suggestions for planning randomised controlled studies regarding the use of hydroxyethyl-starch in critically ill patients - a multidisciplinary statement.** *Crit Care* 2013, **17:**R166.
2. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McgGuinness S, Rajbhandari D, Taylor CB, Webb SAR, the CHEST Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group: **Hydroxyethyl starch or saline for fluid resuscitation in intensive care.** *N Engl J Med* 2012, **367:**1901–1911.
3. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, Madsen KR, Møller MH, Elkjær JM, Poulson LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Søe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quiset L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard A-L, Fabritius ML, Mondrup F, Pott FC, *et al*: **Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis.** *N Engl J Med* 2012, **367:**124–134.
4. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K, German Competence Network Sepsis (SepNet): **Intensive insulin therapy and pentastarch resuscitation in severe sepsis.** *N Engl J Med* 2008, **358:**125–139.

5. Bellmann R, Feistritzer C, Wiedermann CJ: **Effect of molecular weight and substitution on tissue uptake of hydroxyethyl starch: a meta-analysis of clinical studies.** *Clin Pharmacokinet* 2012, **51**:225–236.
6. Mutter TC, Ruth CA, Dart AB: **Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function.** *Cochrane Database Syst Rev* 2013, **7**, CD007594.

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