

LETTER

Existing trial data do not support that hydroxyethyl starch is less harmful when given on more 'correct' indications

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Please see related research by Meybohm et al., <http://ccforum.com/content/17/4/R166>

Meybohm and colleagues hypothesise that so-called 'correct' administration of hydroxyethyl starch (HES) may be beneficial and may provide new guidelines for clinical use of HES, but this is not supported by trial data [1]. In contrast, subgrouping trials according to 'presumable correct indication' does not change the mortality estimate (see Figure 1). There is also very little statistical heterogeneity (I^2) in the recent high-quality meta-analyses on HES indicating harmful effects independent of heterogeneity in trial design.

Several misinterpretations of the Scandinavian Starch for Severe Sepsis/Septic Shock trial publication [2] need correction. First, the exact dose of trial fluid was accounted for in 8,619 of 8,621 (99.98%) trial patient-days. The lack of fluid data after day 3 is thus due to early death or discharge from the ICU.

Secondly, the amount of trial fluid did decrease over time because the percentages of patients who received trial fluid were 94%, 78% and 53% for days 1 to 3, respectively. In fact, the majority of trial fluid was given within the first 38 hours because day 1 only lasted 14 hours (median). Finally, we cannot see the claimed 'conflicts between study protocol specifications and published baseline data', which also must be a misunderstanding.

We strongly discourage clinical algorithms for HES use, which are not supported by data from high-quality trials and which are against the recommendations by independent, scientific and regulatory organs [3-5]. Such algorithms for HES use must undergo testing in trials with low risk of bias before critically ill patients are exposed to potential harm.

Authors' response

Patrick Meybohm, Hugo Van Aken, Andrea De Gasperi, Stefan De Hert, Giorgio Della Rocca, Armand RJ Girbes, Hans Gombotz, Bertrand Guidet, Walter Hasibeder, Markus W Hollmann, Can Ince, Matthias Jacob, Peter Kranke, Sibylle Kozek-Langenecker, Stephan Alexander Loer, Claude Martin, Martin Siegemund, Christian Wunder and Kai Zacharowski

We are grateful to Haase and colleagues for their interest in our paper [1]. We appreciate their amendment to the original paper that 'lack of fluid data after day 3 is thus due to early death or discharge from the ICU' because this very important issue was not previously mentioned [2]. Further, we fully agree with the authors that 'such algorithms for HES use must undergo testing in trials with low risk of bias'.

Regarding the subgroup analysis, however, we disagree with the data analysis. Regarding 30-day mortality in the trial by Siegemund and colleagues, 36 out of 125 patients in the control group and 34 out of 119 patients in the HES group died (M Siegemund, personal communication), resulting in a risk ratio of 0.99 (0.67 to 1.47 95% CI). Taking these data into account would yield a combined risk ratio of 1.12 (0.88 to 1.42 95% CI) in the subgroup of trials with 'high probability of correct fluid indication' (Figure 1). This combined point estimate for mortality does not indicate an increased risk of mortality in the subgroup of probably correct indication. The estimate rather suggests that, assuming the applied

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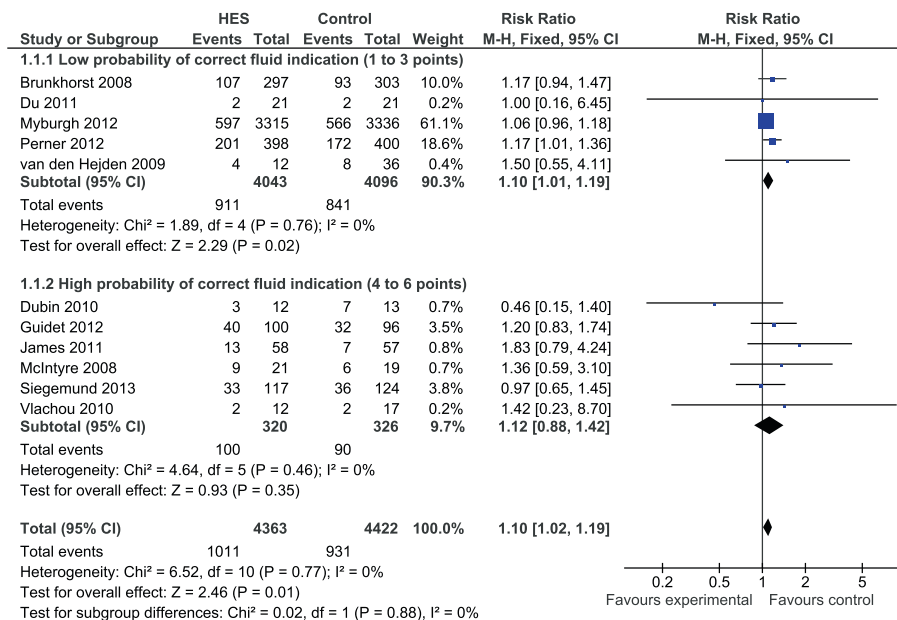


Figure 1 Trial data do not support that hydroxyethyl starch is less harmful when given correctly. Forest plot showing mortality in the trials of hydroxyethyl starch (HES) versus control fluid, which were evaluated by Meybohm and colleagues [1]. Subgroups were defined according to the proposed scoring of 'presumable correct indication' for fluid. Mortality in the intention-to-treat population of James and colleagues was derived from the consort diagram and secondary reports of this trial. Other mortality data were extracted from recent meta-analyses. The present meta-analysis shows comparable mortality estimates in trials with low versus high score; the suggestions by Meybohm and colleagues are thus not supported by trial data. CI, confidence interval; M-H, Mantel-Haenszel. Data from [7-10].

principles of fluid administration are adhered to, the tested interventions are associated with a similar risk for the outcome mortality.

Most importantly, rather than empirically splitting the trials into two groups according to a cutoff value of three points on the scale, we highly recommend performing meta-regression to investigate more appropriately how the different components of the scale did influence treatment effects [6].

In conclusion, algorithms for HES use must undergo testing in trials with low risk of bias, and identification of patients with correct indication is recommended.

Abbreviations

HES: Hydroxyethyl starch.

Competing interests

AP was the sponsor-investigator of the Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial, and NH was a member of the Steering Committee. The 6S trial was funded by the Danish Research Council, the Rigshospitalet Research Council, and the Scandinavian Society of Anaesthesiology and Intensive Care Medicine (the ACTA Foundation). B Braun Medical delivered trial fluid to all sites free of charge. Neither the funders nor B Braun Medical had an influence on the protocol, trial conduct, data analyses or reporting of the 6S trial. AP is head of research in his department, which receives research funds from Fresenius Kabi, Germany, Cosmed, Italy and BioPorto Diagnostics, Denmark. B Braun Medical has covered his travel expenses for presenting 6S trial data at the German Anaesthetic Congress 2012. RGM declares that he has no competing interests.

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