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Clinical Trials in Volume Resuscitation with Hydroxyethyl Starch: Focus on Risk of Bias

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Dear Editor,

Harm from guideline implementation may arise if the recommendations are based on low-quality evidence (1). Ünal and Reinhart provided a review of fluids used for resuscitation in the Turkish Journal of Anaesthesiology and Reanimation, discussing the data on safety and adverse effects and updates from scientific and regulatory bodies of hydroxyethyl starch (HES) (2). Despite this high-quality data documenting the harm caused by HES in vulnerable patient populations, continued licencing of HES was considered a sad day as far as patients' safety is considered.

Ünal and Reinhart (2) criticised the fact that the results of an observational study (RaFTinG), performed between 2010 and 2011 and fully published only in 2018 (3), were presented by the German Society of Anesthesiology and Intensive Care Medicine to the European Medicines Agency as a supporting evidence for the continued licencing of HES (https://www.oegari.at/web_files/dateiarchiv/1143/HES_Open_letter_EC_03.2018pdf.pdf). The study assessed the relationship between intravenous fluid therapy (crystalloids and colloids) and 90-day mortality, intensive care unit mortality and acute kidney injury and renal replacement therapy in patients in the intensive care unit. After a full multivariate adjustment, it reported that 6% HES 130/0.4 has no remarkable negative effects on 90-day mortality (3). Because the unadjusted and baseline-adjusted results clearly exhibited remarkably higher risks of these outcomes in patients treated with HES, owing to potential over-adjustment, it is requested that the fully adjusted results must be interpreted with caution.

However, over-adjustment may not be the only risk of bias of RaFTinG. On the basis of the MINORS scoring tool assessment of observational study quality (4), the research question of RaFTinG is not precisely addressed; no information is given if patient inclusion was consecutive; data were collected prospectively, but if the entire protocol was established before the beginning of the study remains uncertain; crucial protocol information, for example, primary and secondary endpoints, in the trial registry (US National Library of Medicine, registry number NCT01122277) is missing; follow-up period for renal endpoints that were restricted to the length of intensive care unit stay is not sufficiently documented; loss to follow-up was 22.5% (1,022 of 4,545 patients), which exceeds the proportion of 20.1% (707 of 3,523) experiencing the major endpoint of day-90 mortality; and prospective calculation of the study size is missing. In total, the MINORS score of 5 is clearly below the possible ideal score for non-comparative studies of 16 (4). These limitations fundamentally call into question the study's internal and external validity.

Pre-publication of statistical analysis plans is necessary to provide confidence to readers that the analysis is driven by the desire to test a hypothesis, rather than by a data-mining exercise (5). In the case of RaFTinG, with no pre-publication analysis plan and a 5-year period between data collection and reporting, data mining is a typical risk.

Many of the standard critical care interventions were introduced into the clinical practice without evidence from randomised controlled trials and systematic reviews with overall low risk of bias (5). As exemplified with the continued licensing of HES despite the absence of evidence for its benefit, the use of HES based on the results of a biased research carries the risk of ongoing harm to patients.

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Author's Reply

Re: Clinical Trials in Volume Resuscitation with Hydroxyethyl Starch: Focus on Risk of Bias

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Dear Editor,

We thank Prof. Wiedermann for his interest in our article 'Understanding the Harms of HES: A Review of the Evidence to Date'. We agree that the RaFTinG study (1) was limited by several important methodological flaws, including over-adjustment of results and failure to pre-specify endpoints, which raise serious concerns regarding the validity of the analysis and require that the adjusted results be interpreted with caution. As stated by Prof. Wiedermann, primary and secondary outcome measures must be defined and detailed eligibility criteria provided, along with the statistical plan, before a study is conducted so that it is clear whether the published analysis is reliable or has been concocted post-hoc.

Since our review, further compelling evidence has emerged of the harms associated with hydroxyethyl starch (HES). A major randomised controlled trial recently conducted in France assessed the effect of HES 130/0.4 compared with 0.9% saline for intravascular volume expansion on mortality and postoperative complications after major abdominal surgery (2). The Fluid Loading in Abdominal Surgery: Saline vs Hydroxyethyl Starch (FLASH) trial demonstrated that, among patients at risk of postoperative kidney injury undergoing surgery, the use of HES compared with saline resulted in no significant difference in the primary outcome of mortality or major postoperative complications within 14 days after surgery. However, these events were more frequent with HES (139/389 patients; 36%) than with saline (125/386 patients; 32%); the difference did not reach statistical significance (p=0.33) but favoured the saline group (3). The secondary endpoints further indicated that worse outcomes were more frequent with HES. A trend towards increased mortality 28 days after surgery was apparent with HES (4.1%) vs. saline (2.3%), suggesting that the 14-day evaluation period for the primary outcome was too short. Kidney dysfunction within 14 days was also more common in the HES group (22% vs. 16%; p=0.05), as was red blood cell transfusion (19% vs. 12%; p=0.003), possibly reflecting coagulopathy. Volume of study fluid administered and intraoperative fluid balance were lower with HES, but by postoperative day 2 fluid balance was more positive than in the saline group; the early benefit was soon offset by lower diuresis possibly related to early acute kidney injury [3]. The FLASH investigators concluded that "these findings do not support the use of HES for volume replacement therapy in such patients" (2). As noted in the editorial accompanying the FLASH trial publication, the absence of a statistically significant difference in the primary outcome does not indicate the safety of HES (3).

The FLASH trial adds to a growing body of evidence that HES, already contraindicated in patients with sepsis, burn injuries, critical illness or various comorbidites (4), should also be avoided in the operating room in favour of alternative fluid therapy with an acceptable benefit-risk profile. As posted on social media in response to the FLASH trial, it may be that the only remaining appropriate use for HES is to induce coagulopathy in laboratory experiments (5).

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