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Author's Reply

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

Cite this article as: Re: Clinical Trials in Volume Resuscitation with Hydroxyethyl Starch: Focus on Risk of Bias. Turk J Anaesthesiol Reanim 2020; 48(3): 259-60.

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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10.5152/TJAR.2020.110220