EDITORIAL

Hydroxyethyl Starch for Fluid Replacement Therapy in High-Risk Surgical Patients
Context and Caution

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Hydroxyethyl starch (HES) solutions have had a turbulent history as resuscitation fluids.[1,2] There was initial optimism that these products would efficiently expand the intravascular space with a prolonged intravascular half-life and therefore would be "volume sparing," with less edema. However, enthusiasm was tempered when HES solutions were reported to be harmful when administered to critically ill patients, including those with sepsis.[2,3] Despite these concerns, HES is still used in surgery under the premise that lower doses infused under strict protocols would be safe.[4] In this issue of *JAMA*, Futier and colleagues[5] report the results of the FLASH multicenter randomized clinical trial, which assessed the effects of HES vs saline for fluid resuscitation in patients undergoing major abdominal surgery. The primary end point was a composite of death and occurrence of renal, respiratory, cardiovascular, infectious, or surgical complications. Several secondary and exploratory end points were also reported.

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Strengths of the design include the multicenter setting, blinding, and use of a protocolized approach to fluid administration that included optimization of stroke volume index. The primary hypothesis was that HES would decrease the composite end point of death or major postoperative complications from 25% to 15% at 14 days after surgery, a substantial difference considered clinically relevant by the authors. The authors found that the primary end point occurred in 36% of patients (139/389) in the HES group vs 32% (125/386) in the saline group (absolute difference, 3.3%; 95% CI, −3.3% to 10.0%; $P = .33$), a difference that was not statistically significant but that pointed toward the opposite conclusion of the study hypothesis, favoring saline. Important secondary end points also favored saline. In the HES group compared with the saline group, there was more acute kidney injury within 14 days (22% vs 16%, respectively; absolute difference, 5.5%; 95% CI, 0.1%-11.1%) and nominally higher mortality within 28 days (4.1% vs 2.3%; absolute difference, 1.8%; 95% CI, −0.7% to 4.3%), although the difference was not statistically significant. For acute kidney injury, there was no identifiable interaction among baseline kidney dysfunction, treatment group, and occurrence of acute kidney injury, which suggested that HES can cause acute kidney injury even in patients without kidney dysfunction at baseline.

Patients in the HES group received less study fluids (median difference on the day of surgery, 500 mL; 95% CI, 175-824 mL), which resulted in a lower positive fluid balance on the day of surgery. However, as soon as postoperative day 2, when volume of fluids infused equalized between groups, patients in the HES group had lower diuresis and a more positive fluid balance (median difference on day 2, −300 mL; 95% CI, −543 to −57 mL), suggesting that early benefit of lower fluid balance on day 1 was rapidly compensated by a lower diuresis on day 2, which may be related to early acute kidney injury. Additionally, more patients receiving HES than saline received transfusions during the surgical procedure (19% vs 12%; $P = .003$), which could reflect greater hemodilution or even early abnormal effects of HES on coagulation.[6] It is important to highlight that volume of infused fluids and fluid balance have little relevance if not accompanied by robust clinical benefits.

However, some caveats are needed when interpreting the primary conclusion, "Among patients at risk of postoperative kidney injury undergoing major abdominal surgery, use of HES for volume replacement therapy, compared with 0.9% saline, resulted in no significant difference in a composite outcome of death or major postoperative complications within 14 days after surgery."

As noted in 1995 by Altman and Bland,[7] the "absence of evidence is not evidence of absence." The entirety of the results, including the primary and secondary outcomes, need to be considered in interpreting the results of the study. The absence of a statistically significant difference in the primary outcome does not mean that HES is safe. Far from proving safety of HES, the FLASH study corroborates concerns about the use of HES under any circumstances for patients in the operating room or in the intensive care unit.

The results of the FLASH trial could be considered from a Bayesian perspective, assessing the findings in the context of accumulated knowledge from several other randomized trials that compared the effects of HES vs saline in diverse populations. A 2013 systematic review of randomized trials involving both critically ill patients (14 trials; 9247 patients) and perioperative patients (6 trials; 9247 patients) demonstrated an increased risk of acute kidney injury associated with HES vs saline.[8] In another meta-analysis from 2013 involving critically ill patients, HES use was associated with 9% relative risk increase in mortality (28 trials; 10 290 patients) and up to 27% relative risk increase in acute kidney injury (10 trials; 8725 patients).[9] In addition, a 2019 meta-analysis of 55 studies involving critically ill patients (n = 27 036) demonstrated that HES administration was associated with increased risk of mortality.[10] Specifically in the perioperative scenario, a meta-analysis from 2016 of 31 studies and 2287 patients suggested that more coagulation abnormalities and bleeding were associated with HES administration than with administration of

saline or albumin solutions.[6] In summary, HES has demonstrated harmful clinical effects for patients in several settings. The results of the FLASH trial corroborate the detrimental kidney effects of HES and show nominally higher number of deaths consistent with accumulated evidence. Thus, as Futier et al clearly indicate, the findings from their study do not demonstrate any advantage to using HES for volume replacement therapy in high-risk patients undergoing abdominal surgery. Moreover, the accumulated evidence would suggest that HES should perhaps not be used at all.

In conclusion, the FLASH clinical trial suggests that a protocolized surgical optimization approach using HES vs saline resulted in minor physiological benefits on day 1 that vanished soon thereafter. However, important morbidity for patients, specifically acute kidney injury, may be related to HES use. For the primary composite outcome, there is a likelihood that HES is deleterious. It is therefore difficult to justify equipoise for future endeavors in investigation of HES in any scenario given the overwhelming evidence of adverse effects and lack of demonstrable patient-centered benefits.

ARTICLE INFORMATION

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