Hydroxyethyl Starch 130/0.4: Safe for the Kidney in Surgical Patients?

To the Editor:

The safety of hydroxyethyl starch (HES), especially with regard to the kidney, has been on debate for many years.1 Newly reported meta-analyses of randomized controlled trials (RCTs), which included recent large trials of high quality, have moved the controversy much closer to consensus. HES solutions as a class have been shown to increase mortality, acute renal failure, renal replacement therapy (RRT), and severe adverse events compared with other colloids.2,3 Among patients with sepsis, increases attributable to modern HES have been found in mortality, RRT, transfusion, and serious adverse events.4,5

By far, the most extensively investigated modern solution is waxy maize-derived HES 130/0.4. However, similar renal effects have been observed in the 6S RCT of modern potato-derived HES 130/0.42 versus Ringer’s acetate in sepsis.6,7 Thus, in a meta-analysis combining the 6S trial with five RCTs of HES 130/0.4 versus saline (two in sepsis and one each in the intensive care unit, trauma, and cardiac surgery), the pooled relative risk for RRT was 1.27 with a 95% CI of 1.10–1.46.8 For the five RCTs of HES 130/0.4 alone with 6S excluded, the pooled relative risk (1.24; 95% CI, 1.05–1.47) is closely similar.

The accumulated evidence recently prompted an expert panel of the U.S. Food and Drug Administration to conclude that renal failure and bleeding are class effects of HES solutions.9 New randomized trial RRT data have been added to the Prescribing Information for HES 130/0.4 in the United States,† and the U.S. Food and Drug Administration is considering further regulatory action.‡ The European Medicines Agency is currently reevaluating the marketing approvals of HES solutions.‡ Avoidance of HES has been recommended in the latest Surviving Sepsis Campaign Guidelines.9

Therefore, is there still a place for HES in any patient group? This is the question addressed by Martin et al. in a meta-analysis of 17 RCTs evaluating the perioperative infusion of HES 130/0.4 compared with various control fluids.10 Significant differences were not observed in the most extreme postoperative mean values of serum creatinine, the incidence of acute renal failure, or the need for RRT. One interpretation is that surgical patients are not susceptible to HES 130/0.4–mediated renal injury.

An alternative explanation is that renal injury was not detected due to limitations of the meta-analysis. In almost half the included studies, the control fluid was another HES solution or gelatin. Those artificial colloids exhibit their own deleterious renal effects1 and hence are inappropriate comparators that confound the conclusions of the meta-analysis. The accumulated evidence recently prompted an expert panel of the U.S. Food and Drug Administration to conclude that renal failure and bleeding are class effects of HES solutions.‡ Avoidance of HES has been recommended in the latest Surviving Sepsis Campaign Guidelines.9

This was a meta-analysis of small trials exclusively, the majority at single centers. The median number of patients per trial was 65 (range, 11–140). Such trials are more vulnerable to bias. Significant publication bias favoring HES 130/0.4 has recently been shown in a meta-analysis of RCTs.4 Although Martin et al. could not detect publication bias by standard statistical tests, those tests are known to be insensitive in meta-analyses with only small trials.11 Moreover, many included trials in this meta-analysis showed risk of bias due to lack of blinding and inadequate or unclear


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randomization method and allocation concealment. The investigators neglected to present any assessment of quality of included trial or risk of bias.

The statistical power of this meta-analysis to detect an effect on RRT was limited by a very low event rate resulting both from incomplete data and inadequate follow-up. RRT data were not available for 57% of the patients in the meta-analysis, and follow-up was for 5 days or less in most included studies. The median reported time to HES-induced acute renal failure is 16 days,12 therefore, many events were undoubtedly missed. Consequently, only 14 total RRT events were observed in this meta-analysis corresponding to 2.6% of the patients with available RRT data. In contrast, there were 672 RRT events in the meta-analysis of six RCTs corresponding to 8.3% of the patients.5 Furthermore, that meta-analysis was devoid of heterogeneity (F, 0% indicating, contrary to the contention of the Martin et al., that RRT is not a highly variable endpoint in RCTs.

No mechanistic basis is suggested by the investigators for reduced renal risk in surgical patients. The nephrotoxicity of HES is associated with storage in renal tubular cells and osmotic nephrosis.13 It is unclear why surgical patients should be less susceptible to such renal storage of HES and consequent impairment of renal function.

This meta-analysis fails to provide convincing evidence that surgical patients are at low risk of HES 130/0.4–induced renal injury. Rather, it highlights the lack of high-quality data on the safety of perioperative HES 130/0.4 infusion. Such data would be needed before it can be determined whether HES 130/0.4 might have a role to play for fluid management in surgery.

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References


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In Reply:
We thank Drs. Groeneveld et al. and Widermann for their interesting comments on our article.1 Groeneveld et al. made a remark that in CHEST trial, the temporal effects of serum creatinine increase became apparent only between days 1 and 4. Yet the increase was from ±110 to ±116 µmol, which is certainly not clinically relevant. Serum creatinine or creatinine clearance are not perfect biomarkers for renal injury, but no other marker is universally accepted in the field even though many have been studied. Although the CHEST trial2 might be a landmark study, it was conducted in patients in intensive care unit, and we purposely excluded this patient population from our meta-analysis. In the CHEST trial3 only 1,574 of 6,742 patients were randomized after elective surgery (the type of patients we evaluated). When such patients were admitted to intensive care units, it was probably because they suffered intraoperative complications, which may have put them at higher risk of delayed renal complications.

We do not think that the comparison of our work with the meta-analysis by Zarychanski et al.3 is adequate. This