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Confounders *versus* Mediators: An Important Distinction

To the Editor:

We thank Kashy *et al.*[1] for their interesting analysis ("Effect of Hydroxyethyl Starch on Postoperative Kidney Function in Patients Having Noncardiac Surgery)." However, we disagree with some of their methods/assumptions and, in fact, reached different conclusions with the same data. As shown in table 1,[1] the authors did not match patients on intraoperative characteristics. Accordingly, the two groups being compared (intraoperative hydroxyethyl starch [HES] recipients *vs.* noncolloid recipients) were significantly different. *After propensity matching*, nearly twice as many HES recipients were hypotensive (37 *vs.* 20%), nearly three times as many received blood transfusions intraoperatively (14 *vs.* 5%), and nearly one-and-a-half times as many were likely to have received vasopressors (70 *vs.* 45%). In addition, blood loss was twice as much as among noncolloid recipients than among HES recipients (on average 200 *vs.* 100 ml). Hence, these groups are not comparable "at baseline."

As shown in figure 2,[1] blood loss and hypotension are correctly considered confounders (*i.e.*, may be associated with both predictor and outcome) and are controlled for in analysis. In contrast, the authors state that intraoperative vasopressor use and intraoperative blood product transfusion might be mediators (*i.e.*, "mechanisms by which HES administration might cause increased risk of AKI [acute kidney injury]"), implying a position in the causal pathway. Are the authors claiming that AKI (occurring as a result of intraoperative exposure to HES) might occur *via* HES leading to intraoperative vasopressor use and/or blood product transfusion? HES has been shown to influence hemostasis adversely.[2] Are the authors saying that HES-associated AKI may be a result of HES-induced coagulopathy (leading to increased blood product transfusion)?

We believe that intraoperative HES therapy (among patients undergoing major noncardiac surgery) is probably related to clinician-perceived hypovolemia (absolute or relative). Such hypovolemia (rather than receipt of HES *per se*) may lead to both vasopressor use (secondary to hypotension), transfusion, and to AKI, that is, *residual confounding is very likely*. This is apparent in the sensitivity analysis (table 3),[1] as the model with transfusion and vasopressor use as potential confounders showed no effect of HES on AKI (odds ratio, 1.10; 95% CI, 0.96 to 1.25; $P = 0.12$).

The authors might also consider an instrumental variable approach (with calendar time as the instrument). The discontinuation of intraoperative HES use is essentially a "pseudorandom event" such that patients presenting for noncardiac surgery before the HES withdrawal date are probably very similar to patients presenting after this date (of course, all relevant baseline characteristics need to be tabulated to ensure that comparability exists, and where it does not, the parameter that is dissimilar between groups needs to be controlled for if it is a confounder). Such an observational study would emulate the "ideal" randomized controlled trial where essentially similar patients receive different interventions.

Competing Interests

The authors declare no competing interests.

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High-molecular Hydroxyethyl Starch: Is More Data Still Needed?

To the Editor:

With some degree of amazement, we read the article by Kashy *et al.*[1] on the influence of 6% hydroxyethyl starch (HES) 670/0.75 (Hextend; Hospira Inc., USA) on perioperative acute kidney injury in patients undergoing noncardiac surgery. The data are derived from a database of more than 120,000 patients treated in Cleveland hospitals, in which 6% HES 670/0.75 was the most commonly used colloid between 2005 and 2012. After propensity-matched multivariable analysis, the authors found a higher risk of developing more severe acute kidney injury with the use of 6% HES 670/0.75 as compared with sole crystalloids. Notably, a higher rate of acute kidney injury had already been shown with the use of high-molecular HES (6% HES 200/0.62) in critically ill patients with sepsis as compared with gelatin in 2001.[2] Moreover, direct comparison of low-molecular (6% HES 130/0.4) *versus* high-molecular HES

(10% HES 200/0.5) has shown relevant differences on renal function and integrity in the preclinical setting.[3] The safety of 6% HES 130/0.4 with regard to renal function in the perioperative setting was confirmed by clinical studies and a recent meta-analysis.[4,5] As a result, one pharmaceutical company has stopped the production of high-molecular HES in 2013 (Fresenius Kabi Germany). Moreover, in our department, the use of starches other than 6% HES 130/0.4 was already abandoned in 2001 for the above-mentioned reasons. It is therefore surprising that in the present database of Cleveland hospitals, more than 50% of the analyzed patients were treated with high-molecular HES despite the fact that low-molecular preparations have been available since 1999. With respect to this, the clinical relevance of the present study appears to be limited. Finally, the title of the article does not specify the type of starch that was analyzed and is therefore misleading. This is especially true because several recent publications in Anesthesiology highlighted the important differences between HES preparations.[4,6]

With regard to the quality of the propensity-matched analysis, many variables that may serve as potential confounders were numerically higher in the colloid group, even though the predefined level of absolute standard difference was not exceeded. These include intraoperative fluid amounts, intraoperative hypotension, intraoperative blood loss, duration of surgery, blood transfusion, and vasopressor use, which were all higher in the matched colloid as compared with the crystalloid group. It therefore appears that the colloid group was *a priori* at a higher risk of developing acute kidney injury as compared with the crystalloid group. Such intrinsic differences in patient characteristics may hardly be compensated by sophisticated statistical analysis. Finally, despite the known fundamental differences between the various HES preparations,[6] high-molecular HES and waxy maize-derived and potato-derived tetrastarches are not adequately differentiated in the Discussion section.

In summary, the present article investigates a fluid that is known to be unsuitable for modern perioperative care, despite starches with a better renal safety profile are available for perioperative use. Relevant baseline differences may limit valid conclusions from the present dataset.

Competing Interests

The authors declare no competing interests.

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In Reply:

We appreciate Dr. Raghunathan's and Dr. Van Aken's interest in our recent article.[1] Our analysis was based on approximately 29,000 propensity-matched patients who were or were not given intraoperative 6% hydroxyethyl starch (HES) 670/0.75. As Raghunathan *et al.* note, we did not match on intraoperative factors such as hypotension, vasopressor use, and transfusions, and these factors were thus unbalanced. However, we adjusted for hypotension—an obvious confounder—in our subsequent multivariable analysis. A second propensity match that includes all intraoperative factors except vasopressor use and transfusions produced nearly identical results, a roughly 22% increase in the odds of acute kidney injury.

We chose to consider vasopressor use and transfusions to be mediators in our primary analysis "based on our assumption that the administration of hetastarch is mainly triggered by blood loss and that the administration of transfusions and vasopressors happens thereafter and thus might not influence the decision to administer colloids. Thus, vasopressor use and blood transfusions might be mediators."

However, we recognize that vasopressor use and transfusions could also be confounders or (perhaps most likely) both confounders and mediators. We therefore conducted and presented sensitivity analyses in which various factors were considered to be either confounders or mediators. Whereas the conclusion of our primary analysis was that hetastarch administration increases the odds of acute kidney injury approximately 21%, the increases were no longer statistically significant when transfusions or the combination of transfusions and vasopressor use were included as confounding factors. We note, though, that among the eight sensitivity analyses presented in our article, all others remained statistically significant and had roughly comparable treatment effects. Difficulty distinguishing confounders from