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In Reply:

We are very grateful for the impassioned reading of our article[1] by Drs. Kopman and Naguib as their contributions to the field of neuromuscular blockade research are outstanding. We understand their concern that our nuanced conclusion may be misinterpreted in the clinical world, especially one without better neuromuscular blockade reversal alternatives. We specifically performed our study to provide current and meaningful data to identify and/or reinforce best practices for the application of neostigmine in clinical settings where neuromuscular blockade reversal alternatives are unavailable. Our article is a hypothesis-driven study, and we draw our conclusions based on our data. We appreciate their perspective on our article and the opportunity to elaborate on our conclusion and address their question on our control for surgical complexity.

We agree with Drs. Kopman and Naguib that our study did not control for anatomical site of surgery, but we did control for "high-risk surgery" by using a method based on the previously published data.[2] In addition, we addressed the concern of surgical procedure–related confounding with a follow-up study. In the June 2015 edition of Anesthesiology, our laboratory published a retrospective analysis of nearly 50,000 patients who received intermediate-acting nondepolarizing neuromuscular-blocking agents.[3] This large sample size study controlled for both surgical body region and procedure relative value units. We identified a neostigmine dose-dependent increase in the risk of respiratory complications that is eliminated when neostigmine administration is guided by neuromuscular transmission monitoring.

The observed efficacy of neostigmine as a neuromuscular blockade reversal agent in clinical effectiveness studies, where clinicians independently administer and monitor its application, is different than in efficacy studies where clinicians follow strict protocols. Our article reinforces the phenomenon we have previously identified: Clinicians in everyday practice who routinely administer neostigmine reversal without neuromuscular transmission monitoring may be more likely to harm their patients than help.[4,5] Drs. Kopman and Naguib noted this paradox in an earlier publication, "Routine reversal of residual neuromuscular block is less common in parts of Europe than in the US, yet Europeans are less likely to have witnessed postoperative residual paralysis."[6] This observation supports the argument that the clinical use of neostigmine as a reversal agent varies and that this variation in practice may explain the variance in the incidence of residual neuromuscular blockade and postoperative respiratory complications.

The sixteenth-century physician Paracelsus concluded, "All substances are poisons. The right dose differentiates a poison and a remedy." Our data support the intraoperative monitoring of neuromuscular transmission, particularly before tracheal extubation. Intraoperative neuromuscular function should be evaluated by observing the mechanical response to peripheral nerve stimulation whenever a nondepolarizing relaxant is administered; clinical signs (*e.g.*, head lift, hand grip, respiratory effort) are not adequate indicators of depth of neuromuscular blockade. Our data also support the dosing of neostigmine based on train-of-four monitoring.[7]

The clinical take-home message is that the titration of neostigmine must be done carefully and under monitored conditions. We do not seek to have anything in both ways; we seek to have neostigmine administered in the safest way possible.

Competing Interests

Dr. Eikermann, M.D., Ph.D., has filed a patent application for a new drug to reverse the effects of neuromuscular-blocking agents. In addition, he receives funding for investigator-initiated research from Merck, Whitehouse Station, New Jersey, and Massimo, Irvine, California. The other authors declare no competing interests.

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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