

6. Eikermann M, Gerwig M, Hasselmann C, Fiedler G, Peters J: Impaired neuromuscular transmission after recovery of the train-of-four ratio. *Acta Anaesthesiol Scand* 2007; 51:226–34
7. Eikermann M, Vogt FM, Herbstreit F, Vahid-Dastgerdi M, Zenge MO, Ochterbeck C, de Greiff A, Peters J: The predisposition to inspiratory upper airway collapse during partial neuromuscular blockade. *Am J Respir Crit Care Med* 2007; 175:9–15
8. Herbstreit F, Peters J, Eikermann M: Impaired upper airway integrity by residual neuromuscular blockade: Increased airway collapsibility and blunted genioglossus muscle activity in response to negative pharyngeal pressure. *ANESTHESIOLOGY* 2009; 110:1253–60
9. Fuchs-Buder T, Meistelman C, Alla F, Grandjean A, Wuthrich Y, Donati F: Antagonism of low degrees of atracurium-induced neuromuscular blockade: Dose-effect relationship for neostigmine. *ANESTHESIOLOGY* 2010; 112:34–40

(Accepted for publication February 25, 2015.)

### *In Reply:*

We are very grateful for the impassioned reading of our article<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4,5</sup> 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.”<sup>6</sup> 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.<sup>7</sup>

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.

**Matthew J. Meyer, M.D., Nobuo Sasaki, M.D., Matthias Eikermann, M.D., Ph.D.** Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts (M.J.M.). matthewjmeyer@gmail.com

### References

1. Sasaki N, Meyer MJ, Malviya SA, Stanislaus AB, MacDonald T, Doran ME, Igumenshcheva A, Hoang AH, Eikermann M: Effects of neostigmine reversal of nondepolarizing neuromuscular blocking agents on postoperative respiratory outcomes: A prospective study. *ANESTHESIOLOGY* 2014; 121:959–68
2. Brueckmann B, Villa-Urbe JL, Bateman BT, Grosse-Sundrup M, Hess DR, Schlett CL, Eikermann M: Development and validation of a score for prediction of postoperative respiratory complications. *ANESTHESIOLOGY* 2013; 118:1276–85
3. McClean DJ, Diaz-Gil D, Farhan HN, Ladha KS, Kurth T, Eikermann M: Dose-dependent association between intermediate-acting neuromuscular-blocking agents and postoperative respiratory complications. *ANESTHESIOLOGY* 2015; 122:1201–13
4. Grosse-Sundrup M, Henneman JP, Sandberg WS, Bateman BT, Uribe JV, Nguyen NT, Ehrenfeld JM, Martinez EA, Kurth T, Eikermann M: Intermediate acting non-depolarizing neuromuscular blocking agents and risk of postoperative

respiratory complications: Prospective propensity score matched cohort study. *BMJ* 2012; 345:e6329

5. Meyer MJ, Bateman BT, Kurth T, Eikermann M: Neostigmine reversal doesn't improve postoperative respiratory safety. *BMJ* 2013; 346:f1460
6. Naguib M, Kopman AF, Lien CA, Hunter JM, Lopez A, Brull SJ: A survey of current management of neuromuscular block in the United States and Europe. *Anesth Analg* 2010; 111:110–9
7. Kopman AF, Eikermann M: Antagonism of non-depolarising neuromuscular block: Current practice. *Anaesthesia* 2009; 64(suppl 1):22–30

(Accepted for publication February 25, 2015.)

## Confounders versus Mediators: An Important Distinction

To the Editor:

We thank Kashy *et al.*<sup>1</sup> 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,<sup>1</sup> 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,<sup>1</sup> 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.<sup>2</sup> 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),<sup>1</sup> 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 non-cardiac 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.

**Karthik Raghunathan, M.D., M.P.H., Timothy E. Miller, M.B., Ch.B., F.R.C.A., Ali M. Rashid, M.D.** Durham VA Medical Center, Duke University Medical Center, Durham, North Carolina (K.R.). kr118@duke.edu

### References

1. Kashy BK, Podolyak A, Makarova N, Dalton JE, Sessler DI, Kurz A: Effect of hydroxyethyl starch on postoperative kidney function in patients having noncardiac surgery. *ANESTHESIOLOGY* 2014; 121:730–9
2. Kozek-Langenecker SA: Effects of hydroxyethyl starch solutions on hemostasis. *ANESTHESIOLOGY* 2005; 103:654–60

(Accepted for publication February 25, 2015.)

## 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.*<sup>1</sup> 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.<sup>2</sup> Moreover, direct comparison of low-molecular (6% HES 130/0.4) *versus* high-molecular HES