Pulmonary Outcomes and Sugammadex *versus* Neostigmine: Comment

To the Editor:

We have read with great interest the recent article by Kheterpal *et al.*,[1] indicating that sugammadex may be associated with a lower incidence of postoperative pulmonary complications, compared with neostigmine, when used for reversal of neuromuscular blockade in adults.

With a comprehensive matching approach, Kheterpal *et al.* successfully balanced demographic, procedural, and intraoperative factors between groups. However, given the 5-yr study period and a median time difference of 29 months between the neostigmine and sugammadex groups, we contend that it is critical to include an examination of the trend of complications over time informed by the date of intervention, which could be achieved by an interrupted time series analysis.

Numerous studies have demonstrated substantial changes in postoperative pulmonary complication rates over time.[2–4] Although the authors take steps to account for temporal bias, including matching cases and controls that were within 24 months of one another, this may be inadequate. In light of these and other findings, we question whether temporal trends may still be biasing the authors' findings.

Competing Interests

Dr. Freundlich has received grant funding and consulting fees from Medtronic (Minneapolis, Minnesota) for work unrelated to the content of this letter. Dr. Freundlich also holds stock in 3M (St. Paul, Minnesota) and Johnson & Johnson (New Brunswick, New Jersey). The remaining authors declare no competing interests.

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In Reply:

We thank Li *et al.*[1] for their interest and constructive feedback of the sugammadex *versus* neostigmine for reversal of neuromuscular blockade and postoperative pulmonary complications (STRONGER) study. We concur with them that temporal trends and "natural improvement in clinical practice may account for some of the reduction in complications."[2]

Although Li *et al.* cite previous work demonstrating major changes in intraoperative ventilation strategies over time, evidence of any recent, sustained improvement in pulmonary outcomes after noncardiac surgery is limited. Wanderer *et al.*[3] and Schaefer *et al.*[4], cited by Li *et al.*, did not report pulmonary outcomes at all, simply intraoperative

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ventilator settings such as tidal volumes and positive end-expiratory pressure. Memtsoudis *et al.*[5], also cited by Li *et al.*, focused on lung surgery patients between 1988 and 2002, a select group of "noncardiac surgery" that comprised less than 5% of the STRONGER study population. As a result, while we may all hope that recent changes in practice are resulting in sustained improvements in pulmonary outcomes, modern generalizable evidence to this effect is scant.

We agree with Li *et al.* that an interrupted time series analysis is an option to address temporal confounding bias. However, because of the matched cohort design of the STRONGER study, this is not a viable option. Patients receiving sugammadex after its US introduction were matched to similar patients receiving neostigmine before sugammadex introduction. As a result, the temporal exposure of year of surgery is inextricably collinear with sugammadex or neostigmine administration. In the matched analytic cohort, all patients in 2014 and 2015 received neostigmine. Conversely, only 190 (2%) of patients received neostigmine in 2017 and no patients received it in the 2018 dataset. This design allowed us to address the treatment bias of sicker patients undergoing higher-risk surgery receiving sugammadex, consistent with many hospital policies and recently published data.[6] One drawback of the STRONGER study design is that the year of surgery is collinear with the neuromuscular blockade antagonism agent used in 2014, 2015, 2017, and 2018. Therefore, a temporal analysis of the matched cohort is not meaningfully assessing temporal trends.

To address the authors question about trends in outcomes, we have now compared 2014 and 2015 composite pulmonary outcomes in the matched cohort, all of whom received neostigmine. This analysis demonstrated a decrease from 5.3% (351 of 6,630) to 4.9% (486 of 10,016; χ^2 unadjusted odds ratio, 0.91; 95% CI, 0.79 to 1.05; $P = 0.202$). Similar changes were observed in the secondary outcomes of pneumonia (2.6% [170 of 6,630] to 2.3% [232 of 10,016]; χ^2 unadjusted odds ratio, 0.90; 95% CI, 0.74 to 1.10; $P = 0.308$) and respiratory failure (2.2% [146 of 6,630] to 1.9% [188 of 10,016]; χ^2 unadjusted odds ratio, 0.85; 95% CI, 0.68 to 1.06; $P = 0.144$). These data do demonstrate a modest and statistically nonsignificant change in pulmonary outcomes between 2014 and 2015, consistent with Li *et al.*'s letter and our stated limitation that some of the observed improvement in outcome may be associated with temporal improvements. Whether the observed temporal change from 2014 to 2015 was sustained through the remaining study years is impossible to ascertain because the introduction of sugammadex was associated with healthier patients receiving neostigmine at many facilities.[6]

We thank Li *et al.* for their thoughtful commentary and share their desire to elucidate these relationships more clearly.

Competing Interests

Dr. Kheterpal and M. T. Vaughn declare indirect support from Merck & Co., Inc. (Kenilworth, New Jersey), to their organization (University of Michigan, Ann Arbor, Michigan) to support previous research work related to neuromuscular blockade reversal and pulmonary complications.

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