The "True" Risk of Postoperative Pulmonary Complications and the Socratic Paradox: "I Know that I Know Nothing"

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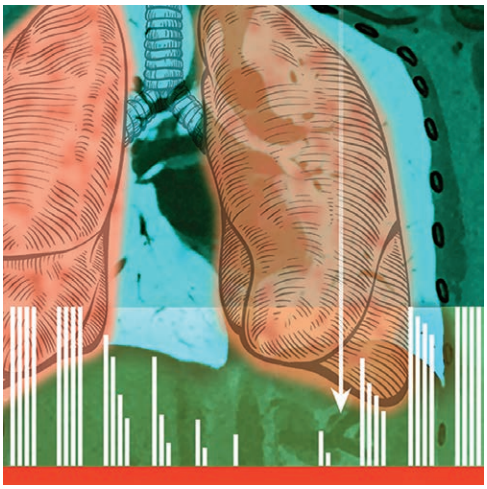
"…what I do not know I do not think I know either." Socrates (c. 470 – 399 BCE)[1]

The development of new medical technologies and pharmaceuticals always rekindles battles between improving quality of care (which assumes clinical effectiveness) and maintaining affordability. The introduction of sugammadex into clinical practice was naturally hailed as a huge advance in the clinicians' ability to better manage aminosteroid nondepolarizing block. While the superiority of sugammadex over neostigmine in short-term biologic benefits such as the speed and reliability of neuromuscular antagonism, particularly from deep and profound levels of block, was never in doubt, clinically relevant, longer-term outcomes that may impact healthcare costs, such as the effects of sugammadex-induced antagonism on patients' postoperative lung function, have been less obvious and based on "beliefs." The debate of whether sugammadex helps in these "outcomes that matter" is important both clinically and financially.



"…[What is the] relationship between neuromuscular antagonists and development of postoperative pulmonary complications[?]"

In this issue of the journal, a retrospective registry analysis explores the association between antagonists and postoperative pulmonary complications.[2] Of the 10,491 patients, 7,800 received neostigmine and 2,691 received sugammadex. A total of 575 (5.5%) patients experienced postoperative pulmonary complications: 5.9% (n = 461) had received neostigmine, and only 4.2% (n = 114) had received sugammadex—but the difference was not statistically significant (adjusted odds ratio, 0.89; 95% CI, 0.65 to 1.22; $P = 0.468$). Regarding specific pulmonary outcomes, 3.2% of neostigmine patients *versus* 2.1% of sugammadex patients experienced postoperative pneumonia, and 1.6% of neostigmine patients *versus* 1.0% of sugammadex patients experienced unplanned intubation—again, differences not statistically significant. A later surgery date was associated with reduced probability of postoperative pulmonary complications; the interrupted time series segmented analysis found no significant trend change in the incidence of any composite postoperative pulmonary complication during the neostigmine period I (before implementation of new Ventilator-Associated Events definitions), the neostigmine period II (presugammadex but after implementation of new Ventilator-Associated Events definitions), and the sugammadex period.

Three previous large-scale investigations focused on clinical outcomes (such as postoperative reintubation, prolonged mechanical ventilation, pneumonia) have explored the important relationship between neuromuscular antagonists and development of postoperative pulmonary complications. The Post-anaesthesia Pulmonary Complications after Use of Muscle Relaxants (POPULAR) study[3] was a prospective observational cohort investigation of 22,803 patients from 28 European countries. A postoperative pulmonary complication was assumed as any adverse pulmonary event within 28 days of surgery.[3] Only 52% of patients received antagonism, and sugammadex was rarely administered. Sugammadex was not associated with a lower incidence of postoperative pulmonary complications.[3] The multicenter, observational, matched-cohort Sugammadex versus Neostigmine for Reversal of Neuromuscular Blockade and Postoperative Pulmonary Complications (STRONGER) trial[4] compared 22,856 patients who were given neostigmine to 22,856 patients given sugammadex. The composite

Image: A. Johnson, Vivo Visuals.

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primary outcome was major postoperative pulmonary complications, defined as pneumonia, respiratory failure, or other pulmonary complications. In contrast with the POPULAR study,[3] the investigators observed that patients who received sugammadex had 30% lower risk of pulmonary complications, 47% lower risk of pneumonia, and 55% lower risk of respiratory failure than patients receiving neostigmine. Similarly, in a single center, before/after analysis, Krause *et al.*[5] examined the effect of antagonism on pulmonary complications, defined as a composite of respiratory failure requiring reintubation or new noninvasive ventilation. A 31% reduction in the incidence of the composite respiratory outcome and a 34% reduction in new noninvasive ventilation were observed after a system-wide change to sugammadex.[5]

Given the large observational registry investigations by Li *et al.*, Kirmeier *et al.*, Kheterpal *et al.,* and Krause *et al.*,[2–5] what definitive conclusions can be derived about the effects of antagonists on postoperative pulmonary complications? Unfortunately, there are important limitations to all four studies. Group assignment was not randomized; therefore, demographic and perioperative risk factors may not have been distributed evenly between groups. Although statistical methodologies were used to match patient groups, the effect of confounding variables may have been significant. Importantly, a change from routine use of neostigmine to sugammadex occurred during the study periods.[2,4,5] Improvements in clinical care during this transition (better management of intraoperative ventilation, implementation of new, less invasive surgical techniques, institution of enhanced recovery after surgery protocols) may account for some of the reduction in pulmonary complications. Additionally, no standard definition of "postoperative pulmonary complication" exists.[2] Determining the effect of sugammadex is complicated by this ambiguity, and further confounded by clinical practices variability that could influence the risk of pulmonary complications: types of surgical procedures performed[6]; anesthetic technique[7,8]; variations in neuromuscular management (type and dose of muscle relaxant[9,10]; use of neuromuscular monitoring[11]; administration of antagonists[12]); and the expansion of early surgical recovery protocols.[13]

A more definitive answer to whether the choice of reversal agent impacts postoperative pulmonary outcomes could be provided by large-scale, randomized controlled clinical trials, but no such data have been published. However, two small, randomized trials have attempted to assess the effect of sugammadex on pulmonary complications as a primary outcome.[14,15] Lee *et al.*[14] randomized 93 thoracic surgery patients to neostigmine or sugammadex, and Togioka *et al.*[15] randomized 200 elderly patients to either reversal agent. In both investigations, pulmonary complications decreased from 40% (neostigmine group) to 33% (sugammadex group).[14,15] Although neither difference was statistically significant, these studies were underpowered to detect differences in pulmonary complications.

Current publications as "trusted evidence" therefore provide conflicting findings. Given this absence of strong evidence from large retrospective[2–5] or small randomized trials,[14,15] what data should guide clinical care? Meta-analyses have reported that compared to neostigmine, sugammadex resulted in a significantly lower risk of residual neuromuscular blockade, fewer respiratory and cardiovascular events, less nausea and vomiting, and fewer signs of residual paralysis, but no differences in serious adverse events.[16,17] Studies have also shown that patients with train-of-four ratios less than 0.9 are at increased risk for hypoxic ventilatory response impairment,[18] are unable to breathe deeply,[19] experience airway obstruction,[20] have diaphragmatic dysfunction,[21] suffer impairment of airway protective reflexes,[22] and are at risk for aspiration.[20] It is logical to conclude that sugammadex use might not only decrease the incidence of residual block, but also reduce the risk of adverse pulmonary events[18,22] and complications[9,23] associated with incomplete neuromuscular recovery. However, definitive proof is illusive.

Several features of the report[2] are clinically relevant. The global rank was a composite of outcomes assessed independently and naturally ordered. Unplanned intubation was most severe (global rank, 3), while a score of 0 indicated no complications. This is critical because postoperative pulmonary complications have a significant financial impact. For instance, a cost analysis of 30-day postoperative complications using the National Surgical Quality Improvement Program reported that the top two complications associated with the highest cost per event were prolonged ventilation ($48,168; 95% CI, $21,861 to $74,476) and unplanned intubation ($26,718; 95% CI, $15,374 to $38,062).[24] If we apply these costs to patients with unplanned intubation (n = 156) during the study period (2010 to 2019) in a single institution, the additional financial burden is an astounding $4,168,008. The authors also remind us that clinical acceptance of practice changes, such as the transition from peripheral nerve stimulators to quantitative monitoring, is both slow and labor intensive.[2] The increase in the rate of quantitative monitor use from 23 to 40% of clinicians[25] was modest, and there are no data confirming that these improvements were sustained. It would be interesting to determine whether the lack of routine quantitative monitoring is partially responsible for the apparent lack of effect of sugammadex (compared with neostigmine) on the incidence of postoperative pulmonary complications. We know that some clinicians erroneously believe that quantitative monitoring is superfluous when using sugammadex. Since sugammadex must be administered in sufficient quantities to inactivate all unbound blocking agent molecules, sugammadex dosing based on clinical criteria or subjective evaluation is likely ineffective,[26] resulting in a higher incidence of residual block and concomitant pulmonary complications.

Despite the inconclusive evidence provided by current literature, we strongly believe that decreasing the risk of residual block by routine quantitative monitoring and judicious administration of sugammadex are paramount to optimizing patient safety.

The battle between "beliefs" will continue into the future, as it is not likely that the "truth" will ever be proven prospectively. In the absence of large pragmatic trials,[27] the two clinician camps (believers and nonbelievers) will dig in deeper into their own trenches, quoting whichever articles best support their practice. This recognition of reality is actually helpful and healthy, as the apparent discrepancy between high-quality (but retrospective), large observational registry investigations will continue to fuel the desire to learn the "truth." The real benefits of sugammadex should be assessed not only by current price, but also by modeling the clinical scenarios in which its use is high and its price is low.[27] The brilliance of the current study[2] is not in describing the "true" relationship between neuromuscular antagonism use and pulmonary outcome; it is in making us realize, like Socrates, that "we know that we know nothing."[1] This realization will make us continue to question, plan, and study that which we do not yet know: the association between sugammadex antagonism and postoperative pulmonary complications.

Competing Interests

Dr. Brull has intellectual property assigned to Mayo Clinic (Rochester, Minnesota); has received research support (funds to Mayo Clinic) from and is a consultant for Merck & Co. (USA); is a principal, shareholder, and chief medical officer in Senzime AB (Uppsala, Sweden); and is a member of the Scientific Advisory Boards for The Doctors Company (Napa, California) and NMD Pharma (Aarhus, Denmark). Dr. Murphy is a consultant for Merck & Co. and has served on the Scientific Advisory Board for Senzime AB (Uppsala, Sweden).

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