Sugammadex and Postoperative Pulmonary Complications

Is Stronger Evidence Required?

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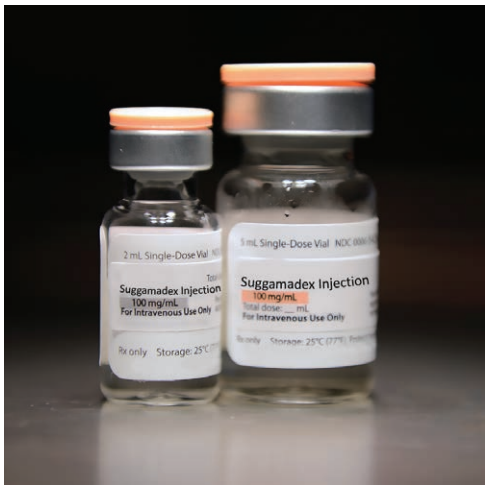
Residual neuromuscular blockade is common and associated with increased risk of airway obstruction, hypoxemia, and postoperative pulmonary complications.[1] Sugammadex reverses moderately deep rocuronium-induced blockade 7 times faster and deep blockade 17 times faster than neostigmine, and only 13 patients need to be treated with sugammadex rather than neostigmine to avoid residual neuromuscular blockade.[2] However, despite this strong biologic rationale for a reduction in postoperative pulmonary complications with sugammadex, evidence from large well-conducted multicenter studies is lacking.



"…choosing sugammadex in combination with quantitative neuromuscular monitoring with the intent of reducing the risk of postoperative pulmonary complication is justifiable."

In this issue of Anesthesiology, Kheterpal *et al.*[3] report the results of the largest observational study to date investigating the association between choice of reversal agent and postoperative pulmonary complications (the sugammadex *versus* neostigmine for reversal of neuromuscular blockade and postoperative pulmonary complications [STRONGER] study). They included 45,712 adults admitted to 12 academic and community hospitals in the United States for elective noncardiac surgery. Of these, 22,856 patients received sugammadex and 22,856 patients received neostigmine for reversal of rocuronium or vecuronium. The incidence of a composite of pneumonia, respiratory failure, pneumothorax, and other major pulmonary complications was 3.5% in the sugammadex group and 4.8% in the neostigmine group (adjusted odds ratio, 0.70; 95% CI, 0.63–0.77; number needed to treat 77 to avoid a major pulmonary complication in one patient in this population). Given the millions of people at risk, the suffering of patients who experience postoperative pulmonary complications, and the financial implications for the healthcare system, this 30% reduction could be practice-changing if it is true.

Kheterpal *et al.* took several steps to reduce the pitfalls associated with observational studies. Because of the cost, services and providers often restrict the use of sugammadex to patients with risk factors for postoperative pulmonary complications (*i.e.*, obesity, pulmonary disease, deep neuromuscular blockade).[4] To mitigate this bias, the neostigmine patients underwent surgery between 2014 and 2015, before sugammadex was approved for use in the United States. To make the two groups as similar as possible, patients were matched on the basis of age, sex, obesity, and comorbidities and surgeries associated with postoperative pulmonary complications. Statistical adjustments were made for preoperative and intraoperative factors showing significant imbalance between the sugammadex- and neostigmine-treated groups. Sensitivity analyses were conducted to determine whether changes to the types of patients included or the coding of postoperative pulmonary complications made a difference to the results, and to determine how susceptible the results were to confounding by unmeasured or unknown factors. The investigators achieved balance between the two groups in many important known confounding factors; their results were stable in a wide range of sensitivity analyses, and the results had low susceptibility to residual confounding. Nevertheless, Kheterpal *et al.* acknowledge that their observational study lacks the power of a large randomized, controlled trial to produce a definitive result.

If a large randomized, controlled trial were to be conducted, what would it look like? A traditional randomized, controlled trial would compare sugammadex and neostigmine under ideal conditions.[5] The patients would be carefully selected to reduce variability. Perioperative drug

Image: J. P. Rathmell.

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administration, temperature management, and ventilation would be protocolized, and quantitative neuromuscular monitoring would be used. Masked study drugs would be administered at a specified state of recovery. Tracheal extubation would only be allowed when strict criteria were met. This careful control would minimize the incidence of postoperative pulmonary complications overall and the difference between the two groups, because all patients would be properly reversed before extubation. Well in excess of 10,000 patients would be required, making this one of the largest and most costly perioperative trials to date.

In the real world, quantitative neuromuscular monitoring and extubation after adequate reversal are not routine.[1,3] Even sustained quality improvement programs are unable to completely change practice.[6] A pragmatic trial testing sugammadex and neostigmine under real-world conditions is therefore justified. Quantitative neuromuscular monitoring would be available and encouraged, but not mandated. A wide variety of patients would be included. Perioperative care would remain at the discretion of anesthesia providers. Unmasked medications would be used, with randomization results revealed to anesthesia providers at the end of surgery. Data collection methodology would be similar to that used by Kheterpal *et al.* (*i.e.*, electronic medical records, administrative databases, and/or registries). The impact of increased variability would likely be moderated by lower rates of residual neuromuscular blockade in the sugammadex group.[2] The results of a pragmatic trial would be generalizable to routine practice in the United States and around the world if sugammadex was more affordable.

Sugammadex remains an expensive drug, out of the reach of many patients and health services that may benefit from its use.[4] Because the current evidence base is inadequate,[2] Kheterpal *et al.* recommend that future evaluations of sugammadex include a cost–benefit analysis.[3] This analysis should be based not only on the current price and existing use: it should also model the situation in which sugammadex is cheap but volume is high. This may reveal a win–win situation for the manufacturer, health services, and patients, and an obligation on all sides to make sugammadex more widely available.

Economics aside, should we wait for the results of a large pragmatic trial before we change our practice? Sugammadex is the best available reversal agent, especially in the real world where appropriate monitoring is not the norm[1] and hard to enforce.[6] There is a very strong rationale that a lower incidence of residual blockade will lead to fewer postoperative pulmonary complications. High-quality observational trials, such as that of Kheterpal *et al.*, suggest a clinically meaningful effect with a number needed to treat that would be even more acceptable if sugammadex were less expensive. Large pragmatic trials are desirable, because they provide the most reliable evidence to guide practice. In the absence of such a trial, choosing sugammadex in combination with quantitative neuromuscular monitoring with the intent of reducing the risk of postoperative pulmonary complication is justifiable.

Competing Interests

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