CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Sugammadex for the Reversal of Neuromuscular Blockade in Surgical Patients: A Review of Clinical Effectiveness and Cost-Effectiveness

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	August 6, 2019
Report Length:	20 Pages

CADTH

Authors: Kendra Brett, Kelly Farrah

Cite As: Sugammadex for the Reversal of Neuromuscular Blockade in Surgical Patients: A Review of Clinical Effectiveness and Cost-Effectiveness Ottawa: CADTH; 2019 Aug. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to Requests@CADTH.ca

Abbreviations

CADTH	Canadian Agency for Drugs and Technologies in Health
ECT	electroconvulsive therapy
NMB	neuromuscular block
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RCT	randomized controlled trial
TOF	train-of-four

Context and Policy Issues

In many procedures requiring intubation neuromuscular blocking agents are administered during anesthesia to facilitate the intubation of the trachea and to optimize the surgical field.1 For short procedures (e.g., less than 30 minutes), a short acting neuromuscular blocking agent, such as succinylcholine, is required for rapid sequence induction and intubation.1 Succinylcholine, a depolarizing neuromuscular blocking agent, produces a reliable neuromuscular block (NMB), has the fastest onset and the shortest duration of all neuromuscular blocking agents, and the recovery of the NMB typically occurs by spontaneous recovery.1

Alternatives to succinylcholine may include using a longer acting neuromuscular blocking agent in conjunction with a reversal agent to produce a short-term NMB. Rocuronium is a non-depolarizing neuromuscular blocking agent with fast onset, which can be used at higher doses for rapid sequence induction and intubation.[1] Sugammadex is a selective relaxant binding agent indicated for the reversal of moderate to deep NMB,[2] with a high affinity for rocuronium.[1,3]

A manufacturer shortage of succinylcholine occurred in Canada in May 2019, and at the time this report was written, the drug shortage was anticipated to last until mid-August 2019.[4] In these circumstances, the use of rocuronium with sugammadex may be an alternative to succinylcholine when there is a need for short acting NMB. Neuromuscular blocking agents and reversal agents are associated with various adverse effects, including residual NMB, myalgias, muscle fasciculations, headache, nausea, and vomiting,[1,3] and it is unclear how the clinical benefits and harms of using rocuronium with sugammadex compare with using succinylcholine alone. In addition, the cost of sugammadex is significantly higher than other common reversal agents (e.g., neostigmine), and it is unknown if sugammadex is cost effective for routine clinical use.[5]

The purpose of this report is to synthesize and critically appraise the available evidence on the clinical effectiveness of rocuronium with sugammadex compared to succinylcholine in patients undergoing surgery who require rapid sequence induction. Additionally, the cost-effectiveness of sugammadex in patients undergoing surgery will be reviewed. This information may be used to inform decision making relating to health policy of the use of sugammadex.

Research Questions

1. What is the comparative clinical effectiveness of rocuronium with sugammadex versus succinylcholine in patients undergoing surgery?

2. What is the cost-effectiveness of sugammadex in patients undergoing surgery

Key Findings

Three randomized controlled trials were identified regarding the clinical effectiveness of rocuronium with sugammadex compared with succinylcholine in patients requiring rapid sequence induction. The evidence consisted of low- to moderate-quality studies conducted in adult patients undergoing three different procedures (i.e., outpatient surgery, bronchoscopy, and electroconvulsive therapy) using different dose combinations for rocuronium, sugammadex, and succinylcholine.

For deep neuromuscular block, moderate-quality evidence from one study suggested that rocuronium with sugammadex had a shorter time to spontaneous respiration and eye-opening as compared with succinylcholine. In contrast, moderate-quality evidence from another study suggested that patients treated with low-dose rocuronium and low-dose sugammadex had longer times to first eye opening compared to patients treated with low-dose succinylcholine for very short procedures.

There was limited low- to moderate-quality evidence that the use of rocuronium with sugammadex was associated with less myalgia, fewer headaches and sore throats, fewer fasciculations, and less myalgia, as compared to succinylcholine.

There was also limited low- to moderate-quality evidence to suggest that rocuronium with sugammadex made no difference compared to succinylcholine with regards to patient satisfaction, extubation time, residual neuromuscular block, post-operative nausea or vomiting, discharge from the operating room or the post-anesthesia care unit, overall adverse events, and serious adverse events.

Evidence from one moderate-quality study suggested that low-dose succinylcholine resulted in better intubation conditions and a shorter time to intubate compared to low-dose rocuronium and sugammadex.

For the most part, the small quantity of heterogenous evidence suggests that the clinical effectiveness of rocuronium with sugammadex in patients requiring rapid sequence induction was better or no different compared with succinylcholine. However, there were three outcomes that favoured low-dose succinylcholine compared to low-dose rocuronium and sugammadex.

One cost-effectiveness evaluation was identified for sugammadex and the evidence was summarized in a previous CADTH report on sugammadex. Sugammadex may lead to economic savings in the hospital setting, however, the certainty of the findings is unclear.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was sugammadex. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and July 5, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1: Surgical patients requiring rapid sequence induction or electroconvulsive therapy (e.g., c-section, morbid obesity, difficult airway Q2: Surgical patients
Intervention	Q1: Rocuronium for blockade followed by sugammadex (Bridion®) for reversal Q2: Sugammadex (Bridion®)
Comparator	Q1: Succinylcholine without reversal Q2: Neostigmine, neostigmine plus glycopyrrolate, neostigmine plus atropine, placebo or no treatment (spontaneous recovery), neostigmine with glycopyrrolate for reversal of high dose >1.0 rocuronium
Outcomes	Q1: Clinical effectiveness (patient benefits and harms) Q2: Cost-effectiveness
Study Designs	Q1: Health technology assessments, systematic reviews, meta-analyses, randomized controlled studies, non-randomized studies Q2: Economic evaluations

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014.

Critical Appraisal of Individual Studies

One reviewer critically appraised the included studies. The randomized studies were critically appraised using the Downs and Black checklist.[6] Economic evaluations were appraised using the Drummond checklist.[7] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 489 citations were identified in the literature search. Following screening of titles and abstracts, 411 citations were excluded and 78 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant reports were retrieved from the grey literatures search. Of these potentially relevant articles, 74 publications were excluded for various reasons, and four publications met the inclusion criteria and were included in this report. These comprised three RCTs, and one economic evaluation. Appendix 1 presents the PRISMA[8] flowchart of the study selection. One of the articles[9] excluded from this report, which described outcomes that did not meet the eligibility criteria (e.g., blood potassium concentrations), was an earlier publication of one of the included studies (Soto et al).[10] This excluded publication[9] was used to supplement missing methodological details from the report by Soto et al.[10]

The one eligible economic evaluation[11] was included in a previous CADTH report on sugammadex,[12] and is only briefly summarized in the current report.

Summary of Study Characteristics

Three RCTs[10,13,14] were identified and included in this review. Detailed characteristics are available in Appendix 2, Table 2.

One economic evaluation[11] was identified; detailed characteristics are available in a previous CADTH report.[12]

Study Design

This report included three RCTs, published in 2016,[10] 2015,[13] and 2014.[14] One multi-centre study included 150 patients.[10] The other two studies recruited patients from single centres, and included 95[13] and 45[14] patients. All three studies were two-arm RCTs.

The cost-effectiveness analysis[11] was published in 2016, and used the health care payer perspective.

Country of Origin

The RCTs were conducted in the US,[10] Germany,[13] and Turkey.[14] The economic evaluation was conducted in Italy.[11]

Patient Population

All three RCTs included adult patients.[10,13,14] Two studies were conducted in hospital settings,[10,13] and the location in the third study was unspecified.[14] Patients in one study were scheduled to undergo elective outpatient surgery under general anesthesia requiring neuromuscular relaxation for tracheal intubation.[10] The patients in the second RCT were scheduled for elective rigid bronchoscopy and tracheobronchial intervention.[13] The patients in the third RCT were undergoing electroconvulsive therapy (ECT) for depression.[14]

The target population of the economic evaluation was adults undergoing surgery with general anesthesia.[11]

Interventions and Comparators

For the intervention of rocuronium to induce the NMB followed by sugammadex to reverse the block, the included RCTs used three different dose combinations for rocuronium and sugammadex. One study used 0.6 mg/kg rocuronium for tracheal intubation and 0.15 mg/kg to maintain the NMB, followed by 4.0 mg/kg of sugammadex for reversal.[10] The second study used 0.25 mg/kg rocuronium, and 0.5 mg/kg sugammadex, which the study authors called ‘low-dose’.[13] The third study used 0.3 mg/kg of rocuronium followed by 4 mg/kg sugammadex for the reversal.[14]

For the comparator of succinylcholine to induce the NMB followed by spontaneous recovery, two studies used a dose of 1 mg/kg succinylcholine.[10,14] The other study used 0.5 mg/kg succinylcholine, which the study authors considered ‘low-dose’.[13]

Outcomes

The three RCTs included some assessment of the time to recovery from NMB. One study calculated the time to recover from NMB for sugammadex using time to train-of-four (TOF) ratio of 0.9, and for succinylcholine using time for the first twitch of the TOF to reach 90% of

baseline; this was monitored using a TOF-Watch SX device.[10] The other two RCTs assessed time to NMB recovery through time to first eye opening,[13,14] and time to spontaneous respiration.[14]

Other efficacy outcomes included time to intubation,[13] intubating conditions,[13] time to extubation,[10] time to discharge from the operating room, time to discharge from the post-anesthesia care unit,[10] and patient satisfaction.[13]

Outcomes related to safety included adverse events in general,[10] residual NMB,[10] fasciculations,[13] post-operative nausea and vomiting,[10] hypotension,[10] and post-operative pain (including myalgia, headache, and sore throat).[10,13,14]

The cost-effectiveness analysis[11] quantified the hospital-related resource savings of reversal of NMB with sugammadex as compared with placebo.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of the included RCTs are provided in Appendix 3, Table 3.

Details regarding the critical appraisal of the economic evaluation can be found in the previous CADTH report.[12] In brief, a number of weaknesses were identified in relation to the economic model which limits the interpretation of the results and their usefulness in decision making.

Randomized Controlled Trials

The quality of the reporting was moderately well done for the RCTs. The RCTs had clear descriptions of the objectives, patient eligibility criteria, interventions and controls. The results were well reported in two studies,[10,13] and in the third report[14] the main outcomes were reported in a way that may limit their interpretation. Adverse events were well reported in one RCT,[10] while the other two RCTs[13,14] did not report on nausea or vomiting, which are common adverse reactions to sugammadex.[3] One study[10] reported when findings were not significant, but did not report actual probability values, thus limiting the overall interpretation of the findings.

In one RCT[10] the method used to measure the main endpoint (i.e., recovery from NMB) was different for the two treatment groups (i.e., recovery of the TOF ratio to 0.9 for sugammadex, and recovery of T_1 to 90% of baseline for succinylcholine). As a result, the primary efficacy endpoint could not be compared between treatment groups resulting in considerable uncertainty in the findings. The authors of the study[10] defended this approach by suggesting that the TOF ratio is not used to assess neuromuscular recovery from succinylcholine. Previous studies comparing sugammadex and succinylcholine for NMB recovery have used the same measurement for both drugs (e.g., recovery of T_1 to 10% of baseline value, recovery of T_1 to 90% of baseline value), instead of the TOF ratio,[15,16] suggesting that Soto et al.[10] could have measured the same endpoint for both interventions and allowed for the comparison between treatment arms.

One study[13] specifically mentioned blinding of the participants and the surgeons, but did not blind the study investigators to the treatments. The other studies did not mention whether the patients or study investigators were blinded to the treatment.[10,14] With regards to blinding of the patients, it is unlikely that the patients would have known which treatment they received as they were unconscious at the time of intervention. Furthermore, it is

unlikely that not being blinded to the intervention would influence the outcomes related to recovery of NMB. There was no cross-over between treatment groups, with all patients receiving the intervention to which they were randomized in all three RCTs, but none of the studies provided enough detail about the randomization process (e.g., block size, when the randomization occurred). It is unclear whether any of the studies adjusted their statistical analysis for multiplicity (i.e., multiple testing of numerous outcomes and time points), which increases the risk of finding false-positive results.

All three studies met their calculated sample size,[10,13,14] however, for one study,[10] the sample size was calculated based on a different primary outcome from a separate publication,[9] thus it is unknown if the study was powered to detect a significant difference in the primary outcome used in the study. All three studies had minimal or no losses to follow-up.[10,13,14] The study participants and care providers in all three RCTs[10,13,14] and the health care setting in two RCTs[10,13] appear to be representative of the people and facilities that would be expected in a clinical context, increasing the external validity of the body of evidence.

Finally, the authors of two studies declared no conflicts of interest.[13,14] For the other study,[10] the authors were supported by, and the study was funded by the manufacturer of sugammadex, however, the report did not address what role the manufacturer may have had in conducting the study or in drafting the manuscript.

Summary of Findings

A detailed summary of findings from the RCTs is provided in Appendix 4, Table 4.

Further details from the economic evaluation can be found in the previous CADTH report.[12]

Clinical Effectiveness of Rocuronium with Sugammadex

Time to Recovery from NMB

The comparative clinical effectiveness of rocuronium with sugammadex versus succinylcholine for the time to recovery of NMB was examined in all three RCTs, although the assessment method differed across studies. One low-quality, industry funded RCT[10] reported time to recovery from deep NMB using different levels of recovery in the treatment groups (i.e., time to TOF ratio of 0.9 for sugammadex, and time for the first twitch of TOF to reach 90% of baseline for succinylcholine), and therefore the geometric mean recovery times cannot be directly compared.

Two moderate-quality RCTs measured time to eye opening to assess recovery from NMB; with one study reporting time to first eye opening,[13] and the other study reported time to eye opening in response to verbal stimuli.[14] The latter RCT also reported time to first spontaneous respiration, as an assessment of recovery time.[14] Neuromuscular recovery time was statistically significantly longer in patients treated with low-dose rocuronium (0.25 mg/kg) and low-dose sugammadex (0.5 mg/kg) compared to patients treated with low-dose succinylcholine (0.5 mg/kg) for bronchoscopy.[13] For the reversal of a deep NMB for patients undergoing ECT, patients who received sugammadex (4 mg/kg) had a statistically significantly shorter time to first spontaneous respiration and time to first eye-opening in response to verbal stimuli, as compared to those treated with succinylcholine.[14]

Time to Intubation

Evidence comparing the time to intubation between rocuronium with sugammadex versus succinylcholine was available from one moderate-quality RCT that used low doses of the drugs in patients undergoing bronchoscopy.[13] Time to intubation (i.e., time from administering the first drug to start of the bronchoscopy) was statistically significantly lower in those treated with low-dose succinylcholine compared to the low-dose rocuronium/sugammadex group.

Intubating Conditions

Intubation conditions were assessed in one moderate-quality RCT comparing low-dose rocuronium and low-dose sugammadex to low-dose succinylcholine for patients undergoing bronchoscopy.[13] Excellent intubation conditions (i.e., conditions for inserting the bronchoscope, vocal cord position, and coughing) were statistically significantly higher in those treated with succinylcholine (46.8%) compared to patients in the rocuronium/sugammadex group (14.6%).

Extubation Time

The time from end of surgery to extubation of the tracheal tube was reported in one low-quality, industry-funded RCT.[10] This study reported no difference in extubation time between groups of patients with deep NMB for outpatient surgery.[10]

Time to Discharge from the Operating Room

Evidence from one low-quality, industry-funded RCT reported no difference in the time from the operating room admission to being ready for discharge from the operating room in surgical patients who were treated with rocuronium with sugammadex, or succinylcholine.[10]

Time to Discharge from the Post-Anesthesia Care Unit

Evidence from one low-quality, industry-funded RCT reported no difference in the time from admission to the post-anesthesia care unit to being ready for discharge from the post-anesthesia care unit in surgical patients treated with rocuronium and sugammadex compared to succinylcholine.[10]

Patient Satisfaction

One moderate-quality RCT found no difference in overall treatment satisfaction when they compared patients treated with low-dose rocuronium and low-dose sugammadex with those treated with low-dose succinylcholine for bronchoscopy.[13]

Fasciculations

Evidence from one moderate-quality RCT comparing low-dose rocuronium and low-dose sugammadex with low-dose succinylcholine for patients undergoing bronchoscopy found that statistically significantly more patients treated with succinylcholine experienced fasciculations (91.5%) than those treated with sugammadex (0%).[13]

Residual NMB

One low-quality, industry funded RCT found no evidence of residual NMB after deep blockade for outpatient surgery in patients treated with rocuronium and sugammadex or succinylcholine.[10]

Adverse Events (overall)

One low-quality RCT reported the number of patients experiencing adverse events and serious adverse events after deep blockade for outpatient surgery in patients treated with rocuronium and sugammadex (87.1% and 1.3%, respectively) or succinylcholine (93.8% and 3.8%, respectively), but no statistical tests were reported to evaluate these findings.[10]

Post-operative Nausea and Vomiting

No significant difference in the proportion of patients experiencing post-operative nausea or vomiting after deep blockade was reported in one low-quality RCT comparing patients treated with rocuronium and sugammadex versus succinylcholine for outpatient surgery.[10]

Procedural Hypotension

One low-quality RCT reported the number of patients experiencing procedural hypotension in patients undergoing deep blockade for outpatient surgery. Fewer patients treated with rocuronium and sugammadex (5.7%) experienced procedural hypotension compared with those treated with succinylcholine (21.3%), but no statistical tests were reported to evaluate these findings in this report.[10] A previous publication of this study reported the difference to be statistically significant.[9]

Post-operative pain

All three RCTs reported some form of post-operative pain (e.g., myalgia, headache, sore throat).[10,13,14] In surgical patients with deep NMB, a low-quality RCT reported similar levels of procedural pain between the sugammadex and succinylcholine groups, but no statistical tests were reported to evaluate these findings.[10] In a moderate-quality RCT, patients undergoing bronchoscopy with low-dose rocuronium and low-dose sugammadex compared with low-dose succinylcholine, statistically significantly fewer patients experienced a sore throat at six and 48 hours after treatment in the sugammadex group compared with the succinylcholine group.[13] The patients treated with low-dose rocuronium and sugammadex also reported statistically significantly less post-operative myalgia than those treated with succinylcholine.[13] In a moderate-quality RCT, patients undergoing deep NMB for ECT treatment who received rocuronium and sugammadex reported statistically significantly less myalgia at two, six and 12 hours, and statistically significantly fewer headaches at two and six hours, as compared with those treated with succinylcholine.[14]

Cost Effectiveness of Sugammadex

The economic evaluation examined the comparative cost-effectiveness of sugammadex versus neostigmine for the reversal of NMB in surgical patients, and found that sugammadex may lead to economic savings in the hospital setting,[11] however, the certainty of the findings is unclear. Full details of the analysis are summarized in the previous CADTH report.[12]

Limitations

There are various limitations with the evidence in the report on the comparative clinical effectiveness of rocuronium with sugammadex versus succinylcholine, and the cost-effectiveness of sugammadex.

A key limitation was the low quantity of identified relevant literature. This report includes three RCTs for the comparative effectiveness of rocuronium with sugammadex versus succinylcholine and one economic evaluation of sugammadex. No high-quality, recent

evidence was identified. In addition, no studies comparing rocuronium with sugammadex versus succinylcholine in pediatric patients were identified, thus it is unknown if the findings are generalizable to the pediatric population.

The body of evidence was heterogenous with regards to the patient population and the doses of rocuronium, sugammadex, and succinylcholine. This report included evidence from three distinct populations (i.e., outpatient surgery, bronchoscopy, and ECT) as well as three different dose combinations of rocuronium and sugammadex and two different doses of succinylcholine, which may limit the ability to compare findings, and the generalizability of the findings.

The body of evidence was also heterogenous with regards to the outcomes that were reported. Numerous efficacy and safety outcomes were captured in the body of evidence, however, except for recovery from NMB, and pain, all other outcomes were reported in one study. For the two outcomes that were assessed in more than one study (i.e., recovery from NMB and pain), inconsistent assessment methods were used, thus making it challenging to form definitive conclusions. Recovery from NMB was measured in different ways across studies, and within one study different levels of recovery were used in the two treatment arms. Pain was also measured with four different outcomes across three studies.

None of the included publications were conducted in Canada or by Canadian authors. It is unknown if the results from the studies conducted outside of Canada are generalizable to Canadian clinical practice as there may be geographic differences between countries in the provision of neuromuscular blocking agents and reversal agents.

The one cost-effectiveness study had limited validity due to short-coming in the economic model, which have been summarized in a previous CADTH report.[12]

Conclusions and Implications for Decision or Policy Making

This report was comprised of three RCTs[10,13,14] and one economic evaluation.[11] This report briefly summarized the economic evaluation, as it was described in a previous CADTH report,[12] and no new economic evaluations meeting the eligibility criteria were identified since the publication of that report.

This report found mixed findings in two moderate quality RCTs comparing recovery from NMB between patients treated with rocuronium and sugammadex versus succinylcholine. In patients who received ECT and deep NMB, those who received with sugammadex had shorter times to spontaneous respiration and eye-opening.[14] In a separate study, patients treated with low-dose rocuronium (0.25 mg/kg) and low-dose sugammadex (0.5 mg/kg) for bronchoscopy had longer times to first eye opening compared to patients who were administered low-dose succinylcholine (0.5 mg/kg).[13] These contrasting results may be due to the depth of the NMB and the doses of the drugs. A third, low-quality RCT also reported recovery time from deep NMB, however, the use of different levels of recovery in the two treatment arms prevented direct comparisons and no conclusions could be made from the findings.[10]

With regards to post-procedural pain, this report found moderate-quality evidence that patients in the low-dose rocuronium and sugammadex group experienced fewer sore throats and myalgia than patients in the succinylcholine group for bronchoscopy.[13] There was also moderate-quality evidence in patients with deep NMB for ECT treatment that patients treated with rocuronium and sugammadex experienced less myalgia and fewer

headaches compared to those treated with succinylcholine.[14] In addition, evidence with a large degree of uncertainty due to a lack of statistical tests reported with these findings suggested that surgical patients with deep NMB experienced similar levels of procedural pain when treated with sugammadex or succinylcholine.[10]

This report also found low- to moderate-quality evidence that rocuronium and sugammadex were associated with additional clinical benefits compared to succinylcholine. Moderate-quality evidence using lower doses of the drugs for bronchoscopy reported that most patients treated with succinylcholine experienced fasciculations, while no patients experienced them following treatment with sugammadex.[13] In addition, there was low-quality evidence that surgical patients treated with rocuronium and sugammadex experienced less procedural hypotension compared with those treated with succinylcholine.[10]

Several outcomes included in this report had no difference between those treated with rocuronium and sugammadex compared to succinylcholine. There was moderate-quality evidence that patient satisfaction did not differ in patients undergoing bronchoscopy with rocuronium and sugammadex versus succinylcholine.[13] There was also low-quality evidence in surgical patients with deep NMB that treatment with rocuronium and sugammadex versus succinylcholine did not differ with regards to extubation time, residual NMB, post-operative nausea or vomiting, discharge from the operating room, discharge from the post-anesthesia care unit, overall adverse events, or serious adverse events.[10] There is a very high level of uncertainty with regards to overall adverse and serious adverse events, as no statistical tests were reported.

Bronchoscopy patients treated with low-dose succinylcholine were reported to have better intubation conditions and shorter time to intubation compared to those treated with low-dose rocuronium and sugammadex, in one moderate-quality RCT.[13]

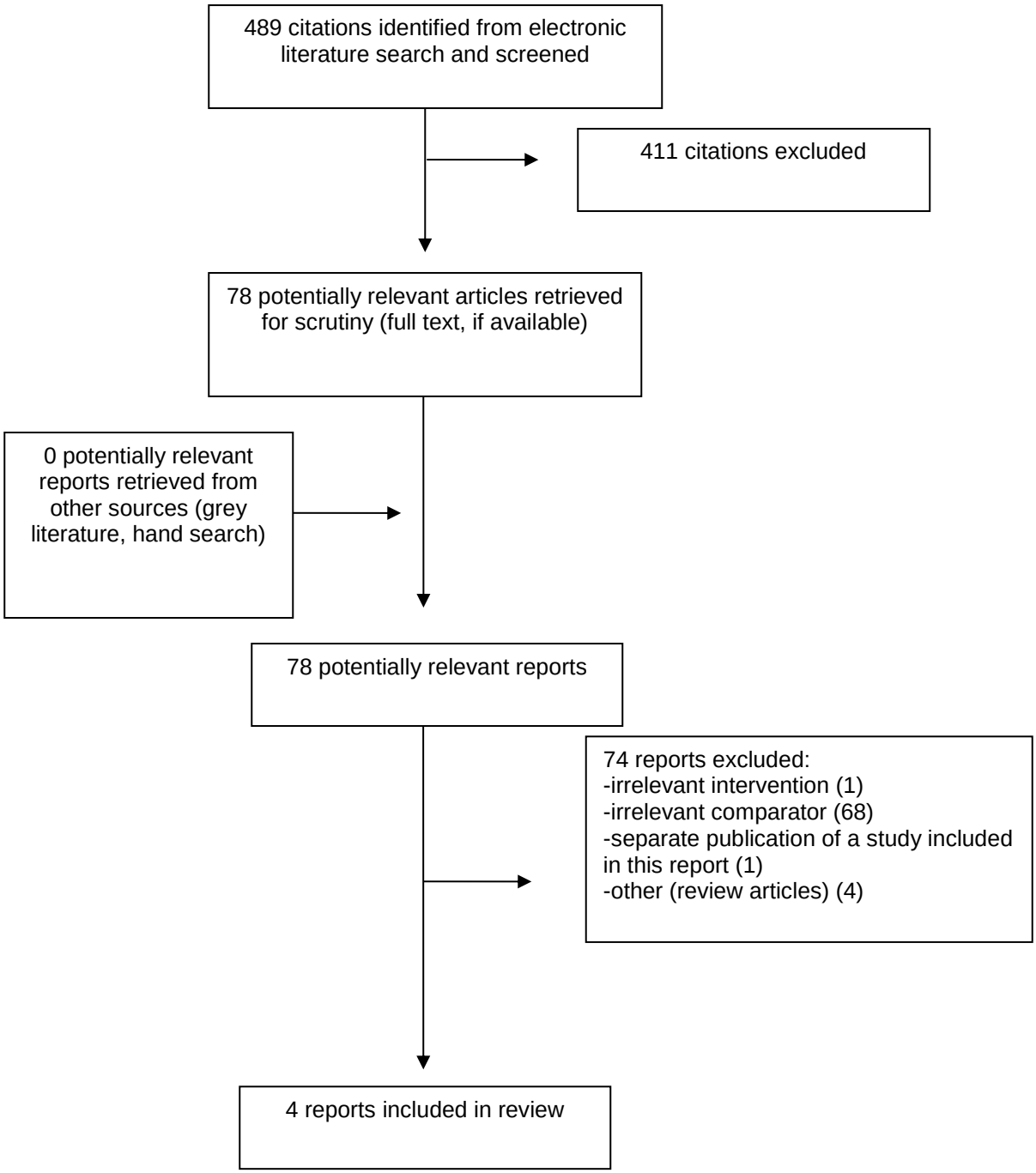
Although limited by the small quantity of heterogeneous low- to moderate-quality evidence, most of the evidence demonstrated that patients treated with rocuronium and sugammadex had outcomes that were better or not worse than patients who were treated with succinylcholine. There was moderate quality evidence to demonstrate that patients undergoing bronchoscopy with low-dose succinylcholine had some better outcomes (i.e., intubating conditions, time to intubation, time to first eye-opening) compared to those treated with low-dose rocuronium and low-dose sugammadex.

The findings highlighted in this report come with a high degree of uncertainty. The limitations of the included studies and of this report should be considered when interpreting the findings. Further well conducted RCTs of surgical patients requiring rapid sequence induction or electroconvulsive therapy addressing rocuronium and sugammadex versus succinylcholine in adult and pediatric patients may help to reduce uncertainty. A well-conducted economic evaluation of sugammadex in the Canadian health care setting would help reduce the uncertainty about the cost-effectiveness of sugammadex in the Canadian context.

References

1. Renew JR, Naguib M. Clinical use of neuromuscular blocking agents in anesthesia. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2019: www.uptodate.com. Accessed 2019 Aug 2.
2. BridionR: solution for infection, 100 mg/mL sugammadex (as sugammadex sodium) [product monograph]. Kirkland (QC): Merck Canada Inc.; 2018: https://www.merck.ca/static/pdf/BRIDION-PM_E.pdf. Accessed 2019 Jul 22.
3. Sugammadex: drug information. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2019: www.uptodate.com. Accessed 2019 Aug 2.
4. Drug Shortages Canada. Drug shortage report for succinylcholine chloride injection. 2019; https://www.drugshortagescanada.ca/shortage/85107. Accessed 2019 Jul 22.
5. Fuchs-Buder T, Meistelman C, Schreiber JU. Is sugammadex economically viable for routine use. *Curr Opin Anaesthesiol.* 2012;25(2):217-220.
6. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf. Accessed 2019 Jul 22.
7. Higgins JPT, Green S, editors. Figure 15.5.a: Drummond checklist (Drummond 1996). *Cochrane handbook for systematic reviews of interventions*. London (GB): The Cochrane Collaboration; 2011: http://handbook-5-1.cochrane.org/chapter_15/figure_15_5_a_drummond_checklist_drummond_1996.htm. Accessed 2019 Jul 22.
8. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
9. Sabo D, Jahr J, Pavlin J, et al. The increases in potassium concentrations are greater with succinylcholine than with rocuronium-sugammadex in outpatient surgery: a randomized, multicentre trial. *Can J Anaesth.* 2014;61(5):423-432.
10. Soto R, Jahr JS, Pavlin J, et al. Safety and efficacy of rocuronium with sugammadex reversal versus succinylcholine in outpatient surgery-a multicenter, randomized, safety assessor-blinded trial. *Am J Ther.* 2016;23(6):e1654-e1662.
11. Carron M, Baratto F, Zarantonello F, Ori C. Sugammadex for reversal of neuromuscular blockade: a retrospective analysis of clinical outcomes and cost-effectiveness in a single center. *Clinicoecon Outcomes Res.* 2016;8:43-52.
12. Sugammadex for the reversal of neuromuscular blockade in adult patients: a review of clinical effectiveness and cost-effectiveness. (*CADTH rapid response: summary with critical appraisal*). Ottawa (ON): CADTH; 2016: https://www.cadth.ca/sugammadex-reversal-neuromuscular-blockade-adult-patients-review-clinical-effectiveness-and-cost. Accessed 2019 Jul 22.
13. Ghezel-Ahmadi V, Ghezel-Ahmadi D, Mangen J, et al. Comparing patient satisfaction and intubating conditions using succinylcholine or low-dose rocuronium for rigid bronchoscopy: a randomized study. *Thorac Cardiovasc Surg.* 2015;63(6):526-532.
14. Saricicek V, Sahin L, Bulbul F, Ucar S, Sahin M. Does rocuronium-sugammadex reduce myalgia and headache after electroconvulsive therapy in patients with major depression? *J ECT.* 2014;30(1):30-34.
15. Lee C, Jahr JS, Candiotti KA, Warriner B, Zornow MH, Naguib M. Reversal of profound neuromuscular block by sugammadex administered three minutes after rocuronium: a comparison with spontaneous recovery from succinylcholine. *Anesthesiology.* 2009;110(5):1020-1025.
16. Kadoi Y, Hoshi H, Nishida A, Saito S. Comparison of recovery times from rocuronium-induced muscle relaxation after reversal with three different doses of sugammadex and succinylcholine during electroconvulsive therapy. *J Anesth.* 2011;25(6):855-859.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Soto et al. 2016[10] **US**	**Study design:** Pre-planned secondary analysis of a randomized, safety-assessor blinded, parallel-group, active-controlled trial **Setting: M**ulticenter, patients enrolled in hospital (13 US sites, 1 Canadian site) between December 2018 and December 2009 **Objective**: Test the hypothesis that prolonged deep relaxation until the end of surgery would be readily reversible without causing delayed recovery or serious AEs when compared with minimal use of a relaxant exclusively for intubation Additional methods were reported in Sabo et al. 2014[9]	**Inclusion criteria: A**dults (> 18 years), American Association of Anesthesiologists Class I, II, or III, body mass index of < 35 kg/m^2, scheduled to undergo an elective outpatient procedure of anticipated short duration (≤1 hour) under general anesthesia requiring neuromuscular relaxation for tracheal intubation **Excluded: I**schemic heart disease or a history of myocardial infarction, difficult intubation expected, neuromuscular disorder impairing NMB, use of a pneumatic tourniquet required during the procedure, significant renal or hepatic dysfunction, personal or family history of malignant hyperthermia, allergy to medications used during general anesthesia, hypersensitive to sugammadex or rocuronium bromide, contraindication to the study drugs, expected to require postoperative admission to intensive care and/or hospital, or expected to receive an intraoperative intravenous administration of fluids containing potassium. **Number of patients:** 150 patients (70 in the sugammadex group, 80 in the succinylcholine group) **Mean age (range):** 40 (18 to 70) in the sugammadex group, 45 (21 to 80) in the succinylcholine group **Sex:** 30% male in the sugammadex group, 34% male in the succinylcholine group	**Intervention:** Rocuronium 0.6 mg/kg for tracheal intubation and 0.15 mg/kg to maintain NMB, followed by 4.0 mg/kg of sugammadex for reversal **Comparator:** Succinylcholine 1.0 mg/kg for tracheal intubation with spontaneous recovery of NMB	**Primary outcome:** Time to recover from deep NMB. Due to drug properties, different monitoring procedures were used: Sugammadex = time to the TOF ratio to 0.9 Succinylcholine = time to T_1 reaching 90% of baseline **Secondary outcomes:** Residual NMB, time to extubation, time until the patient considered ready for discharge from the operating room, and the time from admission to the PACU until patient considered ready for discharge from the PACU, AEs, SAEs, post-operative nausea and vomiting, **Follow-up:** Safety assessment up to 7 days post-surgery
Ghezel-Ahmadi et al. 2014[13] **Germany**	**Study design:** Prospective-randomized, parallel-group, blinded, controlled trial	**Inclusion criteria:** Adults (> 18 years) scheduled for elective rigid bronchoscopy and tracheobronchial intervention.	**Intervention:** Low-dose rocuronium (0.25 mg/kg), and low dose	**Primary outcome:** Patient satisfaction **Secondary outcomes:** Sore

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Setting: Single-centre; patients recruited from the hospital between December 2011 and March 2012. **Objective:** To compare patient satisfaction, incidence of post-operative myalgia, and intubating conditions of succinylcholine or rocuronium for rigid bronchoscopy.	**Excluded:** Known neuromuscular disease, significant hepatic or renal dysfunction, family history of malignant hyperthermia, known allergy to one of the drugs, used, pregnancy, or breastfeeding. **Number of patients:** 95 patients (48 in the sugammadex group, 47 in the succinylcholine group) Four patients lost to follow up in sugammadex group. **Mean age (SD):** 58.3 (13.1) in the sugammadex group, 60.7 (11.6) in the succinylcholine group **Sex:** 54.2% male in the sugammadex group, 66% male in the succinylcholine group	sugammadex (0.5 mg/kg). **Comparator:** Low-dose succinylcholine (0.5 mg/kg)	throat, post-operative myalgia, total induction time, intubating conditions, fasciculations, neuromuscular recovery (time to first eye opening). **Follow-up:** Up to 72 hours after the procedure.
Saricicek et al. 2014[14] **Turkey**	**Study design:** Randomized, controlled trial **Setting:** Single-centre; consecutive patients were recruited (dates and location unspecified) **Objective:** To investigate the effect of succinylcholine and rocuronium-sugammadex complex on the incidence and severity of headaches and myalgia that occur after ECT and to compare the anesthetic recovery time of the patients.	**Inclusion criteria:** Adults (18 to 65 years) with a physical status of American Society of Anesthesiologists physical status I and II who did not undergo ECT in the past were randomized to receive ECT 3 times a week for treatment of major depression to complete an average of 6 to 12 ECT sessions **Excluded:** Patients with a neuromuscular, cardiovascular, and renal disease; pregnant women; and patients with preexisting chronic pain **Number of patients:** 45 patients (21 in the sugammadex group, 24 in the succinylcholine group) **Mean age (SD):** 36.42 (12.33) in the sugammadex group, 41.04 (14.44) in the succinylcholine group **Sex:** 57% male in the sugammadex group, 46% male in the succinylcholine group	**Intervention:** 0.3 mg/kg of rocuronium, plus 4 mg/kg sugammadex **Comparator:** 1 mg/kg succinylcholine	**Primary outcome:** myalgia and headache **Secondary outcomes:** Time to spontaneous respiration, eye-opening response to verbal stimuli. **Follow-up:** Three sessions of ECT per patient, followed for up to 24 hours

AE = adverse event; ECT = electroconvulsive therapy; NMB = neuromuscular block; PACU = post-anesthesia care unit; T_1 = first twitch of the train-of-four; TOF = train-of-four; SAE = serious adverse event

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[6]

Strengths	Limitations
Soto et al. 2016[10]	
• The objectives, interventions, controls, and main outcomes were clearly described • Estimates of variability were provided, where appropriate • Study participants, care providers, and health care settings appear representative of the people and facilities that would be expected in a clinical context • For those who were treated, all patients received the intervention to which they were randomized • Treatment groups well matched for baseline characteristics • No losses to follow up	• Different outcome measures used to assess primary endpoint for the two treatments. • No direct comparison of the primary endpoint between groups • The study was funded by, and the authors of the report were supported by Merck, the manufacturer of Sugammadex. The report does not address conflicts of interest, or what role of the funding body may have had in the conduct of the study or the preparation of the manuscript. • Probability (*P)* values were either not reported at all or they were reported as 'not significant', rather than reporting the actual values • No details reported about the blinding of investigators • Insufficient details about the randomization and allocation concealment process • Sample size calculation based off a different primary outcome
Ghezel-Ahmadi et al. 2014[13]	
• The objective, hypothesis, interventions, controls, and outcomes were clearly described • Treatment groups well matched for baseline characteristics • Minimal losses to follow up • Actual probability (*P)* values were reported • Study participants, care providers, and health care settings appear representative of the people and facilities that would be expected in a clinical context • Surgeons performing bronchoscopy and patients were blinded to the treatment group • All patients received the intervention to which they were randomized • Calculated sample size was met • The authors reported no conflicts of interest	• Adverse events were poorly reported • Study investigators not blinded to treatment • Unable to determine whether all analyses were pre-planned (e.g., subgroups, different time points) • Insufficient details about randomization process
Saricicek et al. 2014[14]	
• The objectives, interventions, controls, and main outcomes were clearly described • Treatment groups well matched for baseline characteristics • Minimal losses to follow up • All patients received the intervention to which they were randomized • Calculated sample size was met • The authors reported no conflicts of interest	• Reporting of the main outcomes was not straightforward, complicating the interpretation of the findings • Did not report nausea or vomiting (adverse events) • Actual probability (*P)* values were not reported • Unable to determine if those assessing the outcomes were blinded to the treatments • Unable to determine whether all analyses were pre-planned (i.e., comparisons across all three sessions) • Insufficient details about the randomization and allocation concealment process

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Soto et al. 2016[10]	
Primary outcome: **Time to recover from deep NMB:** Sugammadex, geometric mean (95% CI) = 1.8 (1.6 to 2.0) minutes Succinylcholine, geometric mean (95% CI) = 10.8 (10.1 to 11.5) minutes Secondary outcomes: **Time from end of surgery to extubation, minutes (median (range)):** 7.0 (0 to 31.0) sugammadex vs. 7.0 (0 to 27.0) succinylcholine; not statistically significant **Time from OR admission to OR discharge ready, minutes (median (range)):** 85.0 (44.0 to 168.0) sugammadex vs. 82.0 (45.0 to 207.0) succinylcholine; not statistically significant **Time from PACU admission to PACU discharge ready, minutes (median (range)):** 76.5 (0.0 to 280.0) sugammadex vs. 76.5 (0.0 to 720.0) succinylcholine; not statistically significant **AEs, total:** 87.1% sugammadex vs. 93.8% succinylcholine **AE, procedural pain:** 64.3% sugammadex vs. 62.5% succinylcholine **AE, procedural hypotension:** 5.7% sugammadex vs. 21.3% succinylcholine (reported as statistically significant, *P* = 0.008 in previous report by Sabo et al. 2014[9] **SAEs:** 1.3% sugammadex vs. 3.8% succinylcholine (none were considered related to the study medication) **Post-operative nausea and vomiting:** 22.9% sugammadex vs. 17.5% succinylcholine; not statistically significant **Residual NMB** No evidence of residual or recurrence of NMB in either treatment group	"*This study suggests that, in the outpatient setting, sugammadex reversal of rocuronium-induced NMB offers a viable alternative to the traditional approach of facilitating tracheal intubation with succinylcholine followed by spontaneous recovery of neuromuscular function." (p1659)* *"It should be noted that, as different levels of recovery were measured in the sugammadex and succinylcholine groups, the geometric mean recovery times cannot be directly compared."* (p1660) "*Health outcome measures, including time from admission to the operating room to the patient being ready for discharge from the operating room and time from admission to the PACU to the patient being ready for discharge from the PACU, were similar between the treatment groups*" (p1660) "*The number of patients reporting AEs overall was similar in both treatment groups"* (p1660)
Ghezel-Ahmadi et al. 2014[13]	
Primary outcome: **Patient satisfaction:** no overall significant difference in the general treatment satisfaction between study groups	"*We found out that patients receiving succinylcholine were less satisfied with the treatment than patients receiving rocuronium and sugammadex. However, the incidence of POM after intervention was significantly higher in the succinylcholine group. Contrary, excellent intubating conditions were significantly higher when succinylcholine was used*." (p529)

Main Study Findings	Authors' Conclusion
Secondary outcomes: **Sore throat,** numeric analog rating scale (NAS)**:** Six hours, no sore throat: 83% sugammadex vs. 50% succinylcholine Six hours, NAS > 4: 4.3% sugammadex vs. 13.7% succinylcholine *P* = 0.01 48 hours, no sore throat: 89.4% sugammadex vs. 63.6% succinylcholine 48 hours, NAS > 4: 0% sugammadex vs. 9% succinylcholine *P* = 0.039 **Post-operative myalgia, present:** Six hours: 2.3% sugammadex vs. 27.3% succinylcholine 24 hours: 4.3% sugammadex vs. 56.8% succinylcholine 48 hours: 4.3% sugammadex vs. 40.9% succinylcholine 72 hours: 4.3% sugammadex vs. 20.5% succinylcholine *P* < 0.001 overall **Time to intubation,** seconds (mean (SD)): 337.0 (82.4) sugammadex vs. 220.6 (44.1) succinylcholine, *P* < 0.001 **Intubating conditions:** Tracheal intubation was successful in all patients Excellent conditions: 14.6% sugammadex vs. 46.8% succinylcholine, *P* = 0.003 Clinically acceptable (excellent and good) conditions: 75% sugammadex vs. 87.2% succinylcholine, *P* = 0.132 **Fasciculations:** 0% sugammadex vs. 91.5% succinylcholine (34% mild, 36.2% moderate, and 21.3% vigorous), *P* < 0.001 overall **Neuromuscular recovery (time to first eye opening),** minutes (mean (SD)): 4.0 (1.8) sugammadex vs. 2.2 (1.9) succinylcholine, *P* < 0.001	
Saricicek et al. 2014[14]	
Primary outcome: **Myalgia and headache, presence:** Sugammadex: first session, no patients experience myalgia or headache; second and third sessions they were reported in the second and sixth hours post treatment, but none at 12 or 24 hours. Succinylcholine: headache and myalgia were experienced at two, six, 12 and 24 hours post treatment following all three sessions. **Myalgia, VAS**: In all three sessions, pain VAS scores were significantly lower at 2, 6, and 12 hours post-treatment in the sugammadex group vs. the succinylcholine group (*P* < 0.001, *P* < 0.001, and *P* < 0.015)	"*Data obtained in this study show that there is a direct relationship between the use of succinylcholine and development of myalgia and headache after ECT*" (p31) "*In conclusion, when rocuronium/sugammadex was compared with succinylcholine, myalgia and headache after ECT were reduced, and patients recovered faster from the neuromuscular blockade*." (p33)

Main Study Findings	Authors' Conclusion
At 24 hours, no statistically significant myalgia VAS score between groups. **Headache, VAS**: In all three sessions, headache VAS scores were significantly lower at 2 and 6 hours post-treatment in the sugammadex group vs. the succinylcholine group ($P < 0.001$, $P < 0.002$) At 12 and 24 hours, no statistically significant headache VAS scores between groups Secondary outcomes: **Time to first spontaneous respiration**, seconds (mean (SD)): First session: 209.76 (34.47) sugammadex vs. 306.67 (57.11) succinylcholine, $P = 0.001$ Second session: 210.71 (34.97) sugammadex vs. 314.63 (44.42) succinylcholine, $P = 0.001$ Third session: 210.24 (40.41) sugammadex vs. 317.58 (35.16) succinylcholine, $P = 0.001$ **Time to eye-opening in response to verbal stimuli**, seconds (mean (SD)): First session: 415.24 (111.42) sugammadex vs. 516.75 (102.76) succinylcholine, $P = 0.002$ Second session: 432.38 (106.53) sugammadex vs. 517.71 (99.21) succinylcholine, $P = 0.012$ Third session: 419.29 (104.56) sugammadex vs. 504.17 (93.34) succinylcholine, $P = 0.004$	

AE = adverse event; ECT = electroconvulsive therapy; NAS = numeric analog rating scale; NMB = neuromuscular block; OR = operating room; PACU = post-anesthesia care unit; SD = standard deviation; SAE = serious adverse event; TOF = train-of-four; VAS = visual analog scale;