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

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Abbreviations

AMSTAR 2	A Measurement Tool to Assess systematic Reviews
CADTH	Canadian Agency for Drugs and Technologies in Health
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
NMB	neuromuscular block
PONV	post-operative nausea and vomiting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RCT	randomized controlled trial
TOF	train-of-four

Context and Policy Issues

In patients undergoing surgery requiring general anesthesia, a neuromuscular blocking agent is often used to paralyze the vocal cords and facilitate intubation of the trachea and improve surgical conditions.[1] Neuromuscular block (NMB) can be moderate or deep, depending on the surgical indication, and it is intended to be temporary.[1] At the conclusion of surgery, the NMB must be reversed, and depending on the depth of the NMB, the recovery may be spontaneous or a reversal agent can be administered.[1]

Rocuronium is a non-depolarizing neuromuscular blocking agent with a rapid to intermediate onset, that is indicated in conjunction with general anesthesia for routine or rapid sequence intubation for adult and pediatric patients.[2] Reversal agents for rocuronium include anticholinesterases and sugammadex.[1] Anticholinesterases work by competing with the neuromuscular blocking agents for acetylcholine receptors and restoring neurotransmission.[1] Neostigmine is a frequently used anticholinesterase with a variable rate of reversal; it is often administered alongside atropine or glycopyrrolate to prevent bradycardia and gastrointestinal side effects, respectively.[1] Sugammadex is a selective relaxant binding agent indicated for the reversal of moderate to deep NMB,[3] with a high affinity for rocuronium.[1,4] Sugammadex encapsulates neuromuscular blocking agents (e.g., rocuronium), inactivating them, resulting in the reversal of the NMB.[3]

The purpose of this report is to synthesize and critically appraise the available evidence on the clinical effectiveness of sugammadex for rocuronium-induced NMB in patients undergoing surgery. This information may be used to inform decision making relating to health policy of the use of sugammadex.

Research Question

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

Key Findings

Three systematic reviews and seven randomized controlled trials were identified regarding the comparative clinical effectiveness of sugammadex versus neostigmine for reversal of rocuronium-induced neuromuscular block. The evidence consisted of low- to high-quality studies conducted in adult and pediatric patients undergoing various surgical

procedures using multiple different dose combinations for rocuronium, sugammadex, atropine, and glycopyrrolate.

Low- to high-quality evidence suggested that sugammadex was associated with a faster time to recovery of neuromuscular block in adult and pediatric patients compared with patients treated with neostigmine. There was also limited evidence of variable quality to suggest that sugammadex was associated with a lower overall risk of adverse events, fewer post-operative pulmonary complications, fewer post-operative abnormalities on chest radiographs, and fewer cases of tachycardia in compared to those treated with neostigmine.

There was evidence of variable quality that demonstrated mixed findings (i.e., some evidence of a beneficial effect of sugammadex, and some evidence of no difference between reversal agents) for the following outcomes: residual neuromuscular block, time to extubation, post-operative nausea and vomiting, dry mouth, bradycardia, and duration of stay in the post-operative anesthesia unit.

There was also limited evidence of low- to high-quality to suggest that sugammadex made no difference compared to neostigmine with regards to post-operative recurarization, the overall quality of recovery, the incidence of pneumonia or lung atelectasis, composite serious adverse events, the need for mechanical ventilation, the risk of bronchospasm, or cases of respiratory depression.

One moderate-quality study suggested that a higher proportion of patients treated with sugammadex experienced hypoxemia compared to those treated with neostigmine.

For the most part, heterogeneous evidence suggests that the clinical effectiveness of rocuronium with sugammadex was better or no different compared with rocuronium and neostigmine. However, there was one adverse event that was higher in patients treated with sugammadex compared to neostigmine.

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	Surgical patients, including those who require rapid sequence induction or electroconvulsive therapy (e.g., c-section, morbid obesity, difficult airway)
Intervention	Rocuronium for blockade followed by Sugammadex (Bridion®) for reversal
Comparator	Rocuronium for blockade followed by one of the following for reversal: neostigmine, neostigmine plus glycopyrrolate, neostigmine plus atropine
Outcomes	Clinical effectiveness (e.g., patient benefits and harms)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or they were published prior to 2014. Primary studies in adult populations were limited to those published in 2018 and 2019. Primary studies that were captured in an included SR were excluded. SRs with full overlap (i.e., the included studies are fully captured in another more recent or more comprehensive SR) were excluded. Primary studies that used vecuronium as the neuromuscular blocking agent were excluded.

Critical Appraisal of Individual Studies

One reviewer critically appraised the included studies. The SRs were appraised using AMSTAR 2,[5] and the randomized studies were critically appraised using the Downs and Black checklist.[6] 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 literature search. Of these potentially relevant articles, 68 publications were excluded for various reasons, and 10 publications met the inclusion criteria and were included in this report. These comprised 3 SRs and 7 RCTs. Appendix 1 presents the PRISMA[7] flowchart of the study selection.

Of the excluded studies, there were 12 RCTs[8-19] that met the inclusion criteria but were excluded based on their publication date (i.e., 2014 – 2017), and four SRs[20-23] that were excluded for having overlapping primary studies with the more comprehensive SRs included in this report. In addition, 12 non-randomized[24-35] studies were identified that were excluded based on their study design, but otherwise met the eligibility criteria. These excluded references may be of potential interest and are provided in Appendix 5

Summary of Study Characteristics

One SR with a narrative synthesis,[36] two SRs with meta-analysis,[37,38] and seven RCTs[39-45] were identified and included in this report. Detailed characteristics are available in Appendix 2, Table 2 and Table 3.

Study Design

One SR with a narrative synthesis published in 2018 was identified that examined neuromuscular blocking agents in patients with obstructive sleep apnea.[36] The scope of this SR[36] was broader than the PICO for this report, and two of the primary studies met the inclusion criteria for this report. Two SRs with meta-analysis[37,38] published in 2017 examined the efficacy and safety of sugammadex compared with neostigmine, but there was no overlap of primary studies as they examined different patient populations. The reviews included literature published prior to January,[38] April, [36] and May[37] 2017; the searches did not include start dates. The SRs with meta-analyses[37,38] included RCTs only, while the other SR with the narrative synthesis[36] included RCTs and observational studies.

This report included seven RCTs[38-45] published between 2017 and 2019, which included between 55 and 304 patients. Five RCTs[39,40,43-45] were single-centre studies, one RCT was a multi-centre study[42], and for one RCT[41] it was unclear.

Country of Origin

The SR with the narrative synthesis[36] was led by authors in Canada but included studies from Turkey and Spain. The SRs with meta-analyses were led by authors in Denmark[37] and China, [38] and neither included primary studies from Canada. The RCTs were conducted in Spain,[40] Turkey, [42] Korea,[43,45] Egypt, [39,41] and Australia.[44]

Patient Population

One SR with a narrative synthesis included adult surgical patients with obstructive sleep apnea.[36] One SR and meta-analysis included adult patients undergoing elective in-patient or day-care surgical procedures. [37] The other SR and meta-analysis included pediatric surgical patients.[38]

Two RCTs included pediatric patients; one included patients aged two to 10 years[40] and the other RCT included patients aged 10 to 25 years.[42] The other five RCTs[39,41,43-45] included adult patients; one of which focused on adults older than 60 years,[43] and another only included women as it was investigating gynecological surgery.[44] The types of surgery included abdominal surgery,[40,41] spinal,[42], eye,[43] liver,[39] colorectal,[45] and gynecological.[44]

Interventions and Comparators

Rocuronium was used to induce NMB in all included publications. The dose of rocuronium was not specified in one RCT,[40] and an initial dose of 0.6 mg/kg was used in the other RCTs,[39,41-45] with some studies also using a smaller maintenance dose of rocuronium to maintain the depth of the NMB.[39,41,45] In the SRs,[36-38] the dose of rocuronium varied across primary studies, and four of the 53 primary studies used a different agent to induce NMB (e.g., vecuronium).

In the SRs,[36-38] the dose of sugammadex varied across the included primary studies and ranged from 2 to 4 mg/kg. Neostigmine was administered with atropine in two SRs,[36,38] and in the third SR,[37] neostigmine was administered alone, with atropine, or with glycopyrrolate, depending on the primary study. There was substantial variation in the dose of neostigmine used across the primary studies included in the SRs (ranged from 0.03 mg/kg to 2 mg/kg neostigmine).

In the RCTs, three studies[40,41,45] used 4 mg/kg of sugammadex and four studies[39,42-44] used 2 mg/kg sugammadex. Neostigmine was administered with atropine[39-42] or glycopyrrolate,[43-45] and the dose of these drugs differed across the RCTs.

Outcomes

Recovery of NMB, defined as time to train-of-four (TOF) ratio > 0.9, was reported in two SRs[37,38] and three RCTs.[39,41,45] Recovery of NMB was also measured using the time to consciousness in one RCT.[42] Other outcomes directly related to the neuromuscular block included residual NMB (i.e., TOF ratio < 0.9),[37,40,41], recurarization,[37,39] the need for an extra dose of reversal agent,[41] and time to extubation.[41,43,44]

In terms of adverse effects, one SR[37] reported composite adverse events and composite serious adverse events. Post-operative nausea and vomiting (PONV) was reported in four studies.[37,38,41,44] With regards to respiratory complications, the following were reported: composite post-operative pulmonary complications,[36] bronchospasm,[38] hypoxemia,[40] respiratory depression,[41] pneumonia,[40] lung atelectasis,[40] and the need for mechanical ventilation.[36] Other outcomes that were reported include bradycardia,[36-38,41] tachycardia,[41] post-operative abnormalities on chest radiograph,[36] duration of stay in the post-operative anesthesia care unit,[39,41] quality of recovery, [43,44] and dry mouth.[41,45]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3, Table 4 and Table 5.

Systematic Reviews and Meta-Analyses

The AMSTAR 2 assessment of the three SRs[36-38] found that two of the SRs[37,38] had well described research questions and inclusion criteria, and both had registered protocols. The other SR with the narrative synthesis[36] did not report having an established protocol, and the research question and inclusion criteria were lacking detail with regards to the comparator group. The SRs[37,38] with meta-analyses only included RCTs, which is recommended for combining results in a meta-analysis,[5] and given that these RCTs reported on adverse events it is not a concern that information was missed by not including non-randomized studies. The SR[36] that used a narrative synthesis to summarize the results included both RCTs and non-randomized studies in order to capture adverse events.

All three SRs[36-38] used a comprehensive literature search strategy and performed the study selection in duplicate. Two of the SRs[37,38] performed the data extraction in duplicate, and the other SR[36] did not report how many people conducted the data extraction. All three SRs[36-38] used the Cochrane Risk of Bias Tool to assess the risk of bias, which assesses risks due to blinding and allocation. Risk of bias in the observational study included in the SR with narrative synthesis[36] was assessed using the Newcastle-Ottawa scale. One SR[37] also assessed the overall quality of the evidence for each outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool, thus improving the understanding of the uncertainty associated with each finding.

For the SRs with meta-analyses, in one SR[38] the statistical heterogeneity was high (i.e., more than 97%), and the statistical heterogeneity remained high in the subgroup analyses by dose of sugammadex. This suggests that there were substantial differences between

the studies and that combining these studies in a meta-analysis may not have been appropriate. The authors of the SR[38] did discuss possible reasons for the heterogeneity, but they did not discuss the potential impact of the heterogeneity on the results of the review. This SR[38] did conduct a subgroup analysis by risk of bias for the primary outcome, however, all of the studies that used neostigmine as the comparator had high or unclear risk of bias (i.e., the only study that was low risk of bias used a placebo as the comparator) and therefore the findings of this subgroup analysis should be interpreted with caution in the context of this CADTH report, due to the high risk of bias. The authors of the other SR with meta-analysis[37] did not assess the potential impact of the risk of bias of the individual studies on the results of the meta-analysis, and the statistical heterogeneity in this SR varied by outcome, ranging from none (e.g., $I^2 = 0\%$ for PONV, bradycardia, and serious adverse events) to high statistical heterogeneity (e.g., $I^2 = 84\%$ for recovery time for 2 mg/kg dose of sugammadex). The authors of both SRs with meta-analyses[37,38] declared no conflicts of interest, and in the other SR with the narrative synthesis[36] one author reported many competing interests but did not address how they managed the potential conflicts of interest in the context of the SR.

Randomized Controlled Trials

In terms of the quality of the reporting, all seven RCTs[39-45] had clear descriptions of the objectives, patient eligibility criteria, interventions and controls. One RCT[41] did not provide sufficient detail about the patient population, and two RCTs[40,43] did not clearly describe or report their primary outcomes. Specifically, in the study by Alday et al.[40] it was unclear whether the residual NMB outcome was measuring using a specific TOF value or the TOF ratio, which affects the interpretation of the finding. In the study by Kim at al.[43] the authors used a nonvalidated Korean translation of a tool to assess the primary outcome, which may limit the validity of the findings. One RCT[41] comprehensively assessed potential adverse events, while the other six RCTs did not report on some of the common adverse reactions to reversal agents, including PONV,[39,40,42,43,45] and residual NMB.[39,42-45] Actual probability values were reported for the statistical tests for all but two of the RCTs, thus limiting the overall interpretation of the findings in these two studies.[39,40]

Patients were described as blinded to the intervention in five RCTs,[40-44] and this was not described in the other two RCTs,[39,45] however, 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. Health care professionals and research staff were described as blinded to the intervention in six of the RCTs,[40-45] and this was not mentioned in the other RCT,[39] however this was unlikely to affect the primary outcome (i.e., time to recovery) as this was monitored with a machine. The randomization and allocation process was well described in five RCTs,[40-44] and the other two RCTs,[39,45] provided insufficient detail about their randomization process (e.g., block size, when the randomization occurred). Patients received the intervention to which they were randomized in six of the RCTs.[39-43,45] In the other RCT[44] there were four patients in the neostigmine group that received sugammadex; two patients received the incorrect drug, and in two instances patients received sugammadex after inadequate reversal with neostigmine. This study was analyzed using the intention-to-treat principle, where patients are included in the analysis based on the drug they were randomized to receive. Two of the RCTs[43,44] examined numerous endpoints (e.g., outcomes broken down into individual components, multiple time points) and may have been at risk of finding false-positive results.

Six RCTs[39-43,45] met their calculated sample size, however, for two of the RCTs[40,45] the sample size was calculated based on primary outcomes that were not included in this report, thus it is unknown if the study was powered to detect a significant differences in the outcomes captured in this report. The other RCT[44] was terminated prior to reaching their calculated sample size, nonetheless, this study included more patients than any of the other RCTs (i.e., more than double the sample size of the study with next highest number of patients). There were minimal to no losses to follow-up in the RCTs.[39-45]

Finally, the primary author of two RCTs[39,44] reported receiving an honorarium from the manufacturer of sugammadex, but neither publication addresses whether this had an influence on the conduct or reporting of the study. The authors of the other RCTs[40-43,45] declared no conflicts of interest.

Summary of Findings

A detailed summary of findings are provided in Appendix 4, Table 6 and Table 7.

Clinical Effectiveness of Sugammadex for the Reversal of Rocuronium in Patients Undergoing Surgery

Recovery of NMB

The comparative clinical effectiveness of rocuronium with sugammadex versus rocuronium with neostigmine for time to recovery of NMB was examined in two SRs[37,38] and four RCTs.[39,41,42,45] Five of the studies assessed this outcome by measuring the time to TOF ratio > 0.9,[37-39,41,45] and the other study measured time to consciousness.[42]

One large SR of adult patients found moderate-quality evidence that a 2 mg/kg dose of sugammadex was statistically significantly faster (10 minutes faster) than a 0.05 mg/kg dose of neostigmine in reversing rocuronium-induced NMB, although there was high statistical heterogeneity in the findings.[37] This review also found low-quality evidence that a 4 mg/kg dose of sugammadex was statistically significantly faster (45 minutes faster) than a 0.07 mg/kg dose of neostigmine in reversing rocuronium-induced NMB in adults, although the evidence was of limited quantity (i.e., 2 RCTs).[37] A SR of pediatric patients also found low-quality evidence that when compared with neostigmine, sugammadex produced a statistically significantly faster time to recovery of the TOF ratio to greater than 0.9, however, this analysis combined different doses of sugammadex and neostigmine.[38] Subgroup analyses by dose of sugammadex (i.e., 2 or 4 mg/kg) also demonstrated that sugammadex resulted in a statistically significantly faster time to recovery, however, both analyses included an RCT that used a placebo as the comparator rather than neostigmine, which limited the certainty of these findings.[38] These analyses in this SR of pediatric patients were all limited by high statistical heterogeneity.

Evidence from three RCTs also reported statistically significantly shorter times to recovery of the TOF ratio > 0.9 with sugammadex as compared to neostigmine for rocuronium-induced NMB.[39,41,45] In one low-quality RCT of adults with liver cirrhosis or healthy liver function, patients treated with 2 mg/kg sugammadex experienced a statistically significantly shorter time to recovery than those treated with 50 mcg/kg neostigmine with 20 mcg/kg atropine.[39] In another low-quality RCT conducted in adults, the time to recovery was statistically significantly faster in patients treated with 4 mg/kg sugammadex to reverse deep NMB compared to 50 mcg/kg neostigmine with 10 mcg/kg glycopyrrolate to reverse moderate NMB.[45] Similarly, in a high-quality RCT, pediatric patients treated with 4 mg/kg sugammadex had a statistically significantly shorter recovery time as

compared with those treated with 0.35 mg/kg neostigmine with 0.02 mg/kg atropine.[41] Another high-quality RCT conducted in pediatric patients also reported a statistically significantly shorter time to consciousness with 2 mg/kg sugammadex when compared to 0.04 mg/kg neostigmine with 0.01 mg/kg atropine.[42]

Residual NMB

One SR examined residual NMB in adult patients treated with any dose of sugammadex compared with neostigmine and found no clinical signs of residual NMB reported in either group across seven RCTs.[37] In pediatric patients, one high-quality RCT also reported no cases of residual NMB in either group (4 mg/kg sugammadex versus 0.35 mg/kg neostigmine with 0.02 mg/kg atropine), however, this study also reported that statistically significantly more patients treated with neostigmine-atropine required a second dose of the recovery agent (n = 8) compared to those treated with sugammadex (n = 1).[41] One moderate quality RCT[40] conducted in adult patients reported statistically significantly fewer patients with residual NMB when treated with 4 mg/kg sugammadex (31%) compared with 40 mcg/kg neostigmine with 10 mcg/kg atropine (71%) immediately after extubation, however, the definition of residual NMB was not clearly defined (i.e., it was unclear if it is TOF < 90% or TOF ratio < 90%) thus limiting the interpretation of this finding. In addition, in one low-quality RCT, two of the women initially treated with neostigmine had to be further treated with a 'rescue dose' of sugammadex following inadequate reversal with neostigmine.[44]

Recurarization

One SR[37] identified 10 RCTs that reported on clinical signs of recurrence of residual NMB in adults patients treated with any dose of sugammadex compared with neostigmine; eight of the RCTs reported no events in either group, and evidence from the other two RCTs showed no difference in clinical signs of recurrence of residual NMB. Another low-quality RCT reported no incidences of post-operative recurarization in adults patients treated with 2 mg/kg sugammadex or 50 mcg/kg neostigmine with 20 mcg/kg atropine.[39] One other moderate-quality RCT reported that one adult patient in the neostigmine group was excluded from the study due to possible recurarization, however, this was only captured as a reason for discontinuing the study and not as an adverse event.[40]

Time to extubation

The comparative clinical effectiveness of rocuronium with sugammadex versus rocuronium with neostigmine for the time extubation was examined in three RCTs. One high-quality RCT found a statistically significantly shorter extubation time in pediatric patients treated with 4 mg/kg sugammadex compared to those treated with 0.35 mg/kg neostigmine with 0.02 mg/kg atropine.[41] Evidence from a moderate-quality RCT conducted adults over the age of 60 undergoing eye surgery also reported a shorter time to extubation in patients treated with 2 mg/kg sugammadex compared with those treated with 1 mg neostigmine and 0.2 mg glycopyrrolate (not body mass dependent).[43] In contrast, evidence from a low-quality RCT conducted in women undergoing gynecological surgery did not see a difference in time to extubation (2 mg/kg sugammadex versus 40 mcg/kg neostigmine with 400 mcg glycopyrronium); this study had the largest sample size (n = 304 women) of all the RCTs, despite failing to reach their calculated sample size.[44]

Quality of recovery

Quality of recovery after reversal of rocuronium-induced NMB was reported in two RCTs.[43,44] Evidence from one moderate-quality RCT showed no difference between groups in

the overall quality of recovery or the nociceptive domain (i.e., pain, nausea and vomiting) of the quality of recovery scale, and a statistically significantly more favorable recovery of the physiological domain of the quality of recovery scale at 15 minutes after surgery in adult patients treated with 2 mg/kg sugammadex compared with those treated with neostigmine (1 mg neostigmine and 0.2 mg glycopyrrolate).[43] However, this study used a nonvalidated Korean translation of the post-operative quality of recovery scale, thus the certainty of the findings is unknown. In another low-quality RCT with a large sample (n = 304 women), no difference in the quality of recovery at 24 hours after surgery was observed in women treated with 2 mg/kg sugammadex as compared with 40 mcg/kg neostigmine with 400 mcg glycopyrronium.[44]

Composite adverse events and composite serious adverse events

The risk of composite adverse events and the risk of composite serious adverse events were reported in one SR conducted in adult patients who were treated with any dose of sugammadex or neostigmine.[37] This SR identified moderate-quality evidence from 28 RCTs that the overall risk of adverse events was significantly lower in patients treated with sugammadex compared with neostigmine, and low-quality evidence 10 RCTs that there is no difference is the overall risk of serious adverse events when comparing sugammadex and neostigmine. In both analyses, three of the RCTs used vecuronium-induced NMB rather than rocuronium-induced NMB, thus the certainty of the evidence in the context of this report in unknown.

PONV

In adults, low-quality evidence from a SR reported that patients treated with sugammadex had a lower risk of PONV compared with patients treated with neostigmine, however, this analysis combined different doses of the reversal drugs.[37] In contrast, one low-quality RCT with a large sample size (n = 304) of women reported similar proportions of patients with PONV in the first six hours after surgery in patients treated with 2 mg/kg sugammadex (49%) compared with those treated with 40 mcg/kg neostigmine and 400 mcg glycopyrronium (51%).[44]

In pediatric patients, a SR included moderate-quality evidence from RCTs with unclear and high risk of bias that found no difference in PONV between patients treated with sugammadex or neostigmine (mixed doses).[38] Conversely, a high-quality RCT reported that pediatric patients treated with 4 mg/kg sugammadex had fewer instances of PONV compared to those treated with 0.35 mg/kg neostigmine with 0.02 mg/kg atropine [41]

Respiratory complications

Comparative evidence on various different respiratory complications was available in two SRs,[36,38] and two RCTs.[40,41] One SR which focused on patients with obstructive sleep apnea, reported evidence from one RCT, that the authors assessed to have unclear risk of bias, that patients treated with sugammadex had fewer post-operative pulmonary complications than those treated with neostigmine.[36] This SR also reported evidence from one non-randomized study, that the authors determined to be fair-quality, that the proportion of patients with post-operative abnormalities on chest radiographs (e.g., atelectasis, pleural effusions) was statistically significantly lower in patients treated with sugammadex as compared with neostigmine, and that patients with obstructive sleep apnea experienced no difference in the need for mechanical ventilation when treated with sugammadex or neostigmine.[36] Another SR identified evidence that they assessed to be very low-quality, that pediatric patients treated with sugammadex had no difference in the

risk of bronchospasm, as compared to those treated with neostigmine.[38] Evidence from one high-quality RCT conducted in pediatric patients reported no cases of respiratory depression following treatment with sugammadex or neostigmine.[41] In adult patients, there was evidence from one moderate-quality RCT that a higher proportion of patients treated with 4 mg/kg sugammadex experienced hypoxemia 24 hours after treatment compared to those treated with 40 mcg/kg neostigmine with 10 mcg/kg atropine, but no difference in the incidence of pneumonia or lung atelectasis.[40]

Dry mouth

In adults, there was evidence from a low-quality RCT that statistically significantly fewer patients treated with sugammadex reported experiencing dry mouth 24 hours after surgery compared with those treated with neostigmine, but there was no difference in dry mouth at one hour or 48 hours after surgery.[45] However, in this study[45] the two reversal agents were used to reverse different levels of NMB (i.e., 4 mg/kg sugammadex to reverse deep NMB compared to 50 mcg/kg neostigmine with 10 mcg/kg glycopyrrolate to reverse moderate NMB), thus there is uncertainty associated with these findings. In pediatric patients, evidence from one high-quality RCT found statistically significantly fewer cases of dry mouth in patients treated with 4 mg/kg sugammadex compared to those treated with 0.35 mg/kg neostigmine with 0.02 mg/kg atropine.[41]

Bradycardia

The comparative clinical effectiveness of sugammadex versus neostigmine for the incidence of bradycardia was reported in three SRs[36-38] and one RCT.[41] One SR reported moderate-quality evidence that adults treated with sugammadex had a statistically significantly lower risk of bradycardia compared with those treated with neostigmine (with no subgroup differences by atropine or glycopyrrolate).[37] However the analysis of this outcome may be associated with some uncertainty as it combined different doses of the reversal drugs and three of the 11 RCTs used vecuronium instead of rocuronium to induce NMB.[37] One SR on patients with obstructive sleep apnea, reported evidence from one RCT that the authors assessed to have unclear risk of bias, that patients treated with sugammadex had a statistically significantly lower incidence of bradycardia than the patients treated with neostigmine with atropine,[36] however, no numerical data accompanied this finding.

In a SR on pediatric patients, low-quality evidence from five RCTs showed that sugammadex resulted in a lower risk of bradycardia compared to treatment with neostigmine with atropine.[38] However, this finding is associated with uncertainty for the following reasons: one of the RCTs used a placebo as the comparator instead of neostigmine; it was reported that several of the studies were excluded in the relative risk calculation due to no incidences of bradycardia in either group, but it does not specify which studies were excluded; and the statistical test does not indicate statistical significance (P = 0.823) but the confidence interval suggests otherwise (i.e., RR = 0.08, 95%CI, 0.01 to 0.42).[38] The incidence of bradycardia was also examined in one high-quality RCT of pediatric patients, which reported no incidence of bradycardia in either group (4 mg/kg sugammadex versus 0.35 mg/kg neostigmine with 0.02 mg/kg atropine).[41]

Tachycardia

One high-quality RCT conducted in pediatric patients reported statistically significantly fewer cases of tachycardia in patients treated with 4 mg/kg sugammadex compared to those treated with 0.35 mg/kg neostigmine with 0.02 mg/kg atropine.[41]

Duration of stay in the Post-operative Anesthesia Care Unit

Two RCTs[39,41] reported on the length of stay in the post-operative anesthesia care unit. In one low-quality RCT of adults with liver cirrhosis or healthy liver function, patients treated with 2 mg/kg sugammadex experienced a statistically significantly shorter duration of stay in the post-anesthesia care unit than those treated with 50 mcg/kg neostigmine with 20 mcg/kg atropine.[39] In a high-quality RCT conducted in pediatric patients, no difference was observed in the discharge time from the post-anesthesia care unit in patients treated with 4 mg/kg sugammadex compared to those treated with 0.35 mg/kg neostigmine with 0.02 mg/kg atropine, however, the time from the reversal agent administration to the arrival in the post-anesthesia care unit was statistically significantly shorter in those treated with sugammadex.[41]

Limitations

There are various limitations with the evidence in this report on the comparative clinical effectiveness of sugammadex versus neostigmine for rocuronium-induced NMB.

A key limitation was the heterogeneity of the body of evidence. Within the three SRs[36-38] there was substantial heterogeneity with regards to the doses of drugs used in the primary studies (e.g., rocuronium, sugammadex, neostigmine, and atropine). One SR with meta-analysis[37] included primary studies with 15 different combinations for the doses sugammadex and neostigmine; further heterogeneity was also present in the variation in doses of rocuronium, or whether neostigmine was administered alone, or in combination with various doses of glycopyrrolate or atropine. While this SR did analyze the primary outcome based on the doses of sugammadex and neostigmine, the calculation for the risk of adverse events and serious adverse events incorporated several different doses of reversal agent.[37] The other SR and meta-analysis[38] included primary studies with four different doses of sugammadex, seven different dose combinations of neostigmine and atropine, and one placebo comparison. Across the seven RCTs,[39-45] there was also two different doses of sugammadex, and six different doses of neostigmine with atropine or glycopyrrolate. In addition, one RCT[45] compared the reversal of deep NMB by sugammadex to the reversal of moderate NMB by neostigmine. It is unclear how the heterogeneity in the doses of the neuromuscular blocking agent and the reversal agents may affect the certainty of the findings, and the generalizability of these findings to the clinical context.

In addition, all three SRs[36-38] were limited by the inclusion of some neuromuscular blocking agents (e.g., vecuronium or cis-atracurium) or reversal agent comparators (i.e., placebo) that were not of interest to this report, thus increasing the uncertainty of the findings in the context of this report. For instance, in the SR by Liu et al.[38] one of the primary studies used a placebo as the comparator (the other nine studies used neostigmine with atropine), thus some of the findings which included this placebo-controlled study in their meta-analysis (e.g., time to reversal for all studies, time to reversal by sugammadex dose, and bradycardia) must be interpreted with caution. Similarly, in the SR by Hristovska et al.[37] there were three RCTs included in the safety meta-analyses which used vecuronium to induce NMB, leading to greater uncertainty in some findings (i.e., composite adverse and serious adverse events). In the other SR,[36] the included observational trial included some patients in which cis-atracurium was used to induce NMB in the neostigmine group. Excluding evidence from the SRs that mixed ineligible neuromuscular blocking agents or comparators with eligible ones (ineligible and eligible within the context of this report) would have excluded a large proportion of the

findings of this report, thus these findings were retained for the report, however it is important to interpret these findings appropriately.

Only one of the included publications was conducted by authors in Canada,[36] however, neither of the relevant primary studies included in this SR were conducted in Canada. 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.

Conclusions and Implications for Decision or Policy Making

This report was comprised of three SRs[36-38] and seven RCTs[39-45] regarding the comparative clinical effectiveness of sugammadex versus neostigmine for reversal of rocuronium-induced NMB.

For recovery of NMB, there was evidence from six low- to high-quality studies that consistently demonstrated that sugammadex resulted in a faster recovery from NMB than neostigmine in both adult[37,39,45] and pediatric patients.[38,41,42] This report also identified four additional benefits of using sugammadex to reverse NMB compared with using neostigmine.[36,37,41] In adult patients, when compared to neostigmine, there was also moderate-quality evidence that patients treated with sugammadex had a lower overall risk of adverse events,[37] and low-quality evidence that adult patients with obstructive sleep apnea had fewer post-operative pulmonary complications, and fewer post-operative abnormalities on chest radiographs.[36] There was also evidence from a high-quality study conducted in pediatric patients that those treated with sugammadex experienced fewer cases of tachycardia in compared to those treated with neostigmine.[41]

For six of the outcomes included in this report, the findings reported across different publications were mixed; with some evidence suggesting that sugammadex was better than neostigmine, and other evidence suggesting no difference between the reversal agents. None of the outcomes with mixed findings demonstrated better results for patients treated with neostigmine. With regards to residual NMB, there was evidence from a low-quality study that fewer adult patients experienced residual NMB when treated with sugammadex compared with neostigmine,[40] however, most of the evidence identified in this report found no cases of NMB in adult[37] and pediatric patients.[41] Evidence from moderate- to high-quality studies found that pediatric[41] and adult[43] patients treated with sugammadex had shorter extubation times compared with those treated with neostigmine, as well as a low-quality study in adult patients that there was no difference in time to extubation between reversal agents.[44] For PONV, in adult and pediatric patients, there was low- to high-quality evidence that patients treated with sugammadex had either fewer cases of PONV[37,41] or a similar number of cases of PONV,[38,44] compared with patients treated with neostigmine. There was also evidence from low- to high-quality studies of fewer cases of dry mouth after surgery following treatment with sugammadex compared with neostigmine in pediatric patients[41] and adult patients (at 24 hours),[45] however, in the adult patients, no difference in dry mouth was observed at one hour or 48 hours after surgery.[45] In addition, low- to moderate-quality evidence reported that adult[36,37] and pediatric[38] patients treated with sugammadex have a lower risk of bradycardia compared with those treated with neostigmine with atropine, however, in pediatric patients, two studies reported no incidences of bradycardia in either group.[38,41] Finally, with regards to duration of stay in the post-anesthesia care unit, in adults, one low-quality study suggested that adult patients treated with sugammadex experienced a shorter duration of

stay than those treated with neostigmine,[39] while a high-quality study in pediatric patients reported no difference in the discharge time from the post-anesthesia care unit between groups.[41]

For eight outcomes in this report, the included evidence found no difference between the two reversal agents. In adult patients, there was low- to moderate-quality evidence that patients treated with sugammadex experienced no difference in post-operative recurarization,[37,39] the overall quality of recovery,[43,44] the incidence of pneumonia or lung atelectasis,[40] composite serious adverse events,[37] or the need for mechanical ventilation,[36] as compared with patients treated with neostigmine. In pediatric patients, there was very low- to high-quality evidence that patients treated with sugammadex experienced no difference in the risk of bronchospasm,[38] or cases of respiratory depression (none in either group),[41] when compared to patients treated with neostigmine.

This report identified one outcome for which sugammadex had a worse result than neostigmine. One moderate-quality study conducted in adult patients reported that a higher proportion of those treated with sugammadex experienced hypoxemia 24 hours after surgery compared to those treated with neostigmine.[40]

Although limited by the heterogeneity with regards to the doses of drugs used in the primary studies and the mostly low- to moderate-quality evidence, most of the evidence included in this report demonstrated that patients treated with sugammadex had outcomes that were better or no different than patients treated with neostigmine. Time to reversal of the NMB was consistently faster in patients treated with sugammadex as compared to neostigmine. Several outcomes had mixed findings, with evidence supporting either a beneficial effect of sugammadex or no difference between reversal agents. One adverse event, hypoxemia, was higher in adult patients treated with sugammadex.

The findings highlighted in this report come with a moderate degree of uncertainty. The limitations of the included studies and of this report should be considered when interpreting the findings. Further research focused on specific doses of the reversal agents or the depth of the neuromuscular block may help to reduce some of the uncertainty.

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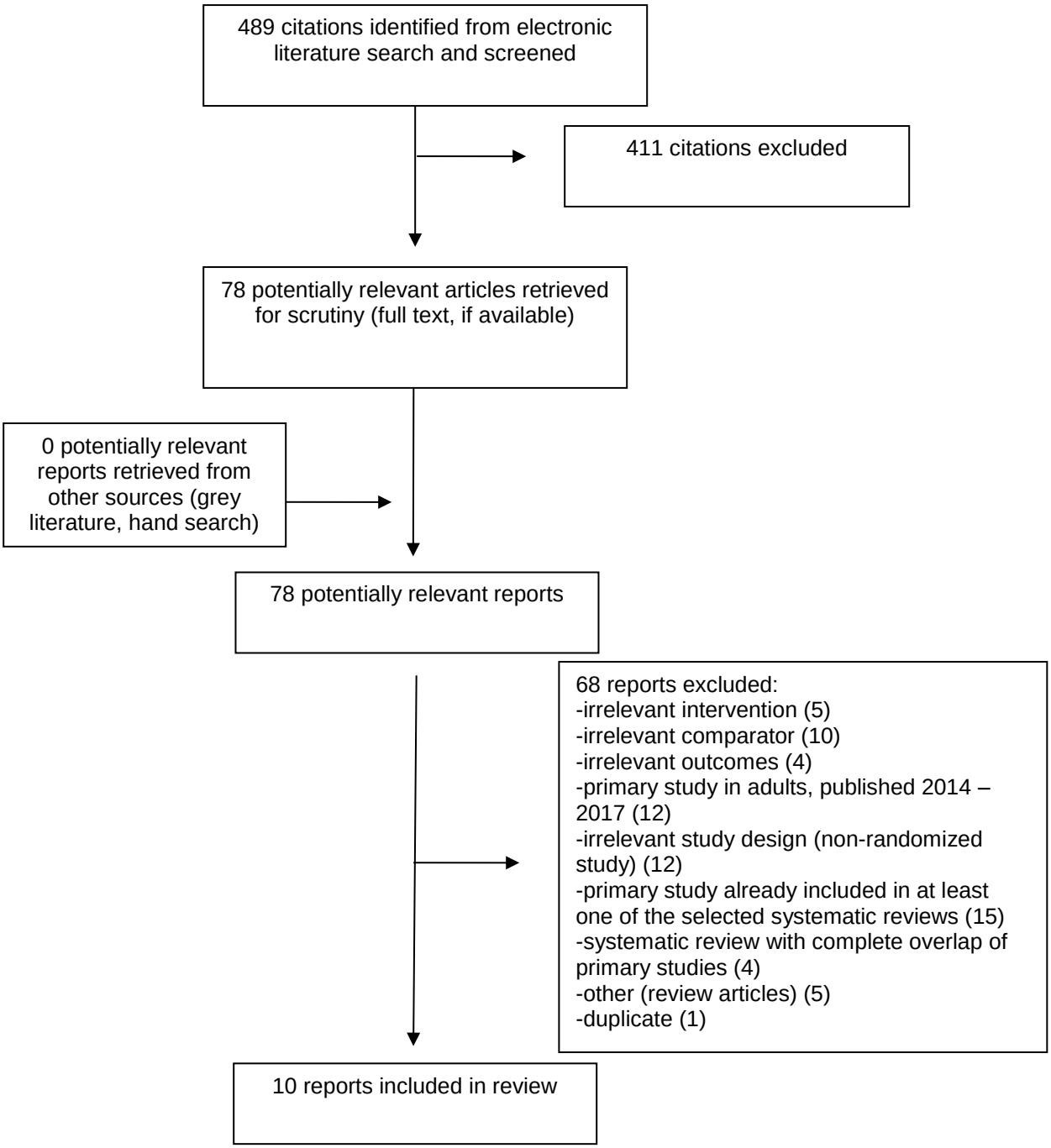
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Health Technology Assessments and Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Literature Searched, Numbers of Primary Studies Included, and Objective	Eligibility criteria	Intervention and Comparator	Clinical Outcomes, Length of Follow-Up
Hafeez 2018[36] **Canada**	**Search:** Databases searched included MEDLINE (1946 to April 4, 2017), ePub ahead of print, MEDLINE in-process, and other non-indexed citations (up to April 4, 2017), Embase (1947 to April 4, 2017), Cochrane Central Register of Controlled Trials (up to February, 2017), Cochrane Database of Systematic Reviews (2005 to April 4, 2017), PubMed (1946 to April 4, 2017), Web of Science (1900 to April 4, 2016), Scopus (1960 to April 4, 2017), ClinicalTrials.Gov (up to April 6, 2017), WHO ICTRP (up to April 6, 2017). **Included studies:** 1 RCT 1 observational cohort **Objective:** To determine whether the choice of NMB reversal agent affects the risk of postoperative complications in patients with OSA. (Includes another objective that is not relevant to this report)	**Inclusion criteria:** adult surgical patients (≥18 years) with OSA, patients given NMB drug and reversal agents intraoperatively; reports on postoperative adverse events, published in English and RCTs or observational cohort studies **Exclusion criteria:** Case reports, review articles, studies lacking information on OSA status, studies with not information of post-operative pulmonary complications or residual NMB.	Rocuronium or cis-atracurium to induce NMB **Intervention:** Sugammadex RCT = 2 mg/kg Observational study: 4 mg/kg **Comparator:** Neostigmine RCT = 0.04 mg/kg plus 0.02 mg/kg atropine Observational study: 0.04 mg/kg plus 0.02 mg/kg atropine	**Outcomes:** Post-operative pulmonary complications, bradycardia, post-operative abnormalities on chest radiograph, need for mechanical ventilation. **Follow-up:** not reported
Hristovska 2017[37]	**Search:** The following databases were searched until May 10, 2017: Cochrane Central Register of	**Inclusion criteria:** Adults (>18 years), American Society of Anesthesiologists status I to IV, who had received nondepolarizing	Mostly rocuronium for NMB. Three RCTs in the safety assessment used vecuronium for NMB.	**Primary outcomes:** 1. Recovery time from T2 to TOF ratio > 0.9 (for 2

<table>
<tr><th>First Author, Publication Year, Country</th><th>Literature Searched, Numbers of Primary Studies Included, and Objective</th><th>Eligibility criteria</th><th>Intervention and Comparator</th><th>Clinical Outcomes, Length of Follow-Up</th></tr>
<tr><td>Denmark</td><td>Controlled Trials (CENTRAL); MEDLINE (WebSPIRS Ovid SP, 1950 onwards); and Embase (WebSPIRS Ovid SP, 1980 onwards).
Also searched trial registries, references lists of reviews, and contacted main authors in the field.

Included studies: 41 RCTs (31 included in the meta-analysis)

Objective: Compare the efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade caused by non-depolarizing neuromuscular agents in adults.</td><td>neuromuscular blocking agent for an elective in-patient or day-case surgical procedure. RCTs comparing sugammadex vs. neostigmine.

Exclusion criteria: Pediatric patients, healthy volunteers, or participants not undergoing surgical procedures. Observational studies. Studies with non-standard designs, such as cross-over or cluster-randomized trials. Trials that compared sugammadex and neostigmine vs. only placebo or no intervention.</td><td>Intervention: Sugammadex

Comparator: Neostigmine

Breakdown of doses for the 41 RCTs:<table><tr><th># of RCTs</th><th>Sugammadex (mg/kg)</th><th>Neostigmine</th></tr><tr><td>2</td><td>2</td><td>0.04 mg/kg</td></tr><tr><td>15</td><td>2</td><td>0.05 mg/kg</td></tr><tr><td>2</td><td>2</td><td>0.07 mg/kg</td></tr><tr><td>3</td><td>2</td><td>2.5 mg</td></tr><tr><td>1</td><td>3</td><td>0.03 mg/kg</td></tr><tr><td>1</td><td>4</td><td>0.04 mg/kg</td></tr><tr><td>4</td><td>4</td><td>0.05 mg/kg</td></tr><tr><td>3</td><td>4</td><td>0.07 mg/kg</td></tr><tr><td>1</td><td>4</td><td>Not reported</td></tr><tr><td>1</td><td>4</td><td>1 to 2 mg/kg</td></tr><tr><td>1</td><td>Not reported</td><td>Not reported</td></tr><tr><td>4</td><td>Several</td><td>several</td></tr><tr><td>1</td><td>2 ideal body weight vs. corrected body weight</td><td>50 mcg/kg ideal body weight vs. corrected body weight</td></tr><tr><td>1</td><td>4 ideal body weight</td><td>70 mcg/kg lean body weight</td></tr><tr><td>1</td><td>2 corrected body weight</td><td>50 mcg/kg corrected body weight</td></tr></table>Note: neostigmine administered alone, or with atropine or glycopyrrolate.</td><td>mg/kg doses of sugammadex)
2. Recovery time from post-tetanic count 1 to 5 to TOF ratio > 0.9 (for 4 mg/kg doses of sugammadex)

Secondary outcomes: adverse events (composite and specific), serious adverse events

Follow-up: Not reported.</td></tr>
<tr><td>Liu 2017[38]

China</td><td>Search: The following databases were searched until January 20, 2017: MEDLINE (PubMed),</td><td>Inclusion criteria: RCTs comparing sugammadex with either neostigmine or a placebo in pediatric patients who were</td><td>Rocuronium for NMB. (No included studies used vecuronium)
0.6 mg/kg dose in 9 RCTs
0.45 mg/kg dose in 1 RCT</td><td>Primary outcomes: Time from administration of reversal agent to TOF ratio > 0.9</td></tr>
</table>

First Author, Publication Year, Country	Literature Searched, Numbers of Primary Studies Included, and Objective	Eligibility criteria	Intervention and Comparator	Clinical Outcomes, Length of Follow-Up
	EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science™. Also searched grey literature and checked the reference lists of relevant reviews. **Included studies:** 10 RCTs **Objective:** To examine whether sugammadex can be used to reverse rocuronium or vecuronium, compared with neostigmine or placebo in pediatric patients undergoing general anesthesia.	undergoing surgery involving the use of rocuronium or vecuronium. No language or date restrictions. Different doses of sugammadex were included. **Exclusion criteria:** Studies comparing sugammadex with sugammadex combined with neostigmine.	**Intervention:** Sugammadex 2 mg/kg dose in 6 RCTs 4 mg/kg dose in 3 RCTs 1 RCT used doses of 0.5, 1, 2 and 4 mg/kg (with placebo comparator) **Comparator:** Neostigmine with atropine (9 RCTs) or placebo (1 RCT) Doses: 5 mcg/kg neostigmine with 2.5 mcg/kg atropine (1 RCT) (suspected by SR authors to be reported incorrectly, as it is far lower than recommended) 30 mcg/kg neostigmine with 10 mcg/kg atropine (1 RCT) 40 mcg/kg neostigmine with 20 mcg/kg atropine (1 RCT) 50 mcg/kg neostigmine with 10 mcg/kg atropine (1 RCT) 50 mcg/kg neostigmine with 20 mcg/kg atropine (2 RCTs) 50 mcg/kg neostigmine with 25 mcg/kg atropine (2 RCTs) 60 mcg/kg neostigmine with 20 mcg/kg atropine (1 RCT)	**Secondary outcomes:** Drug-related adverse events. **Follow-up:** Not reported.

OSA = obstructive sleep apnea; NMB = neuromuscular block; RCT = randomized controlled trial; SR = systematic review; T2 = second twitch; TOF = train-of-four;

Table 3: 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
Alday 2019[40] **Spain**	**Study design:** Randomized controlled trial **Setting:** Single tertiary care university hospital; study conducted from July 2015 to July 2016. **Objective:** To compare the change in forced vital capacity one hour after reversal with neostigmine or sugammadex among patients undergoing major abdominal surgery.	**Inclusion criteria:** All patients scheduled for major abdominal surgery (liver resection, pancreatectomy, gastrectomy, or any type of colectomy), with the use of a postoperative epidural analgesia. **Excluded:** Refusal to participate, admission to postoperative recovery unit under mechanical ventilation, hypersensitivity to any of the drugs, severe asthma or mild asthma under treatment, myocardial infarction or coronary occlusion three months prior to surgery, myasthenia gravis, emergency surgery, pulmonary fibrosis, or very severe chronic obstructive lung disease **Number of patients:** 126 (62 in the sugammadex group, 64 in the neostigmine group) **Mean age (SD):** 65.9 (12.0) in the sugammadex group, 69.9 (13.0) in the neostigmine group **Sex:** 52% male in the sugammadex group, 50% male in the neostigmine group	NMB with rocuronium and monitored by TOF. **Intervention:** 4 mg/kg sugammadex **Comparator:** 40 mcg/kg neostigmine with 10 mcg/kg atropine	**Outcomes:** Residual NMB, lung atelectasis, **h**ypoxemia, pneumonia. **Follow-up:** up to 24 hours after surgery
Biricik 2019[42] **Turkey**	**Study design:** Randomize, double-blind, prospective trial **Setting:** Multi-centre; patients recruited from Cukurova University and Ortopedia hospital between December 15, 2017 and August 15, 2017. **Objective:** To compare the effects of intravenous sugammadex and neostigmine plus atropine reversals on	**Inclusion criteria:** Patients aged 10 to 25 years, undergoing spinal surgery for scoliosis, with American Society of Anesthesiologists physical status I to II. **Excluded:** Unconscious patients, American Society of Anesthesiologists physical status III to IV, and history of preoperative neurologic disorders. **Number of patients:** 60 patients (30 in sugammadex group, 30 in the neostigmine group) **Mean age (SD):** 16.6 (4.29) in the sugammadex group, 16.1 (4.97) in the neostigmine group	NMB with rocuronium (0.6 mg/kg) and monitored by TOF. **Intervention:** 2 mg/kg sugammadex **Comparator:** 0.04 mg/kg neostigmine with 0.01 mg/kg atropine	**Primary outcome:** time-to-consciousness (time to obeying verbal commands) **Secondary outcomes:** TOF scores during the wake-up test, complications **Follow-up:** immediately post-reversal

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	time‐to‐consciousness (described as the time to obeying verbal commands after reversal of NMBAs), during the intraoperative wake‐up test in subjects undergoing spinal surgery.	**Sex:** 40% male in the sugammadex group, 60% male in the neostigmine group		
Kim 2019[43] **Korea**	**Study design:** Single-blind, prospective, randomized controlled trial **Setting:** Single-centre; patients recruited from hospital between February and July 2017 **Objective:** Evaluate the influence of reversal of NMB with sugammadex or neostigmine on postoperative quality of recovery following a single bolus of rocuronium under general anesthesia	**Inclusion criteria:** Adults (> 60 years) undergoing pars plana vitrectomy under general anesthesia **Excluded:** Neuromuscular disease; significant renal or hepatic dysfunction; history of malignant hyperthermia; allergic reaction to sugammadex or rocuronium; on medication which can affect NMB, body mass index >30 kg/m^2 , and psychological or language problems that may impede the assessment. **Number of patients:** 84 patients (40 in sugammadex group, 44 in the neostigmine group) **Median age (range):** 64 (61.5 to 67) in the sugammadex group, 63.5 (60.5 to 66) in the neostigmine group **Sex:** 41% male in the sugammadex group, 35% male in the neostigmine group	NMB with rocuronium (0.6 mg/kg) **Intervention:** 2 mg/kg sugammadex **Comparator:** 1 mg neostigmine with 0.2 mg glycopyrrolate	**Primary outcome:** Recovery of the physiological domain of the Postoperative Quality Recovery Scale (PostopQRS). Physiological domain includes: blood pressure, heart rate, temperature, respiration, airway, agitation, consciousness. **Secondary outcomes:** Nociceptive domain of the PostopQRS (includes pain intensity, nausea and vomiting), overall recovery, time-to-extubation, **Follow-up:** 1 day post-operatively
Abdulatif 2018[39] **Egypt**	**Study design:** Randomized controlled trial; 4-arms. Two groups of patients with liver cirrhosis. Two groups of patients with normal liver functions. **Setting:** Single-centre, patients recruited from National Liver	**Inclusion criteria:** Adults (18 to 60 years) undergoing liver resection, either with normal liver function or liver cirrhosis. **Excluded:** Neuromuscular disease, body mass index more than 35 kg/m^2, renal impairment, receiving medications known to affect	NMB with rocuronium (0.6 mg/kg initial dose), and NMB maintained with 0.15 mg/kg top-up doses, as needed. **Intervention:** 2 mg/kg sugammadex	**Primary outcome:** Time to recovery of TOF ratio of 0.9 **Secondary outcomes:** incidence of post-operative recurarization (recurrence of NMB; a decrease in TOF ratio to <0.9 after full

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Institute, Menoufiya University from November 1 2014 to end date unspecified. **Objective:** Compare the neuromuscular recovery times with the use of sugammadex and neostigmine as antagonists of moderate rocuronium-induced neuromuscular block in patients with child "A" liver cirrhosis and patients with normal liver functions undergoing liver resection	neuromuscular transmission, allergic to study medications, major intraoperative blood loss **Number of patients:** 55 patients (14 in the normal liver-sugammadex group, 14 in the normal liver-neostigmine group, 13 in the liver cirrhosis-sugammadex group, 14 in the liver cirrhosis-neostigmine group) **Mean age (SD):** 34.1 (12.1) in the normal liver-sugammadex group, 33.4 (12.9) in the normal liver-neostigmine group, 60.2 (5.3) in the liver cirrhosis-sugammadex group, 58.0 (5.5) in the liver cirrhosis-neostigmine group **Sex:** 57% in the normal liver-sugammadex group, 79% in the normal liver-neostigmine group, 69% in the liver cirrhosis-sugammadex group, 71% in the liver cirrhosis-neostigmine group	**Comparator:** 50 mcg/kg neostigmine with 20 mcg/kg atropine	recovery had been documented), duration of stay in the PACU **Follow-up:** until discharge from surgical ICU
Koo 2018[45] **South Korea**	**Study design:** Prospective, randomized controlled trial. Patients randomized to moderate or deep NMB. **Setting:** Single-centre; patients recruited from Seoul National University Bundang Hospital (dates not reported) **Objective:** Evaluate the effects of deep NMB on surgical conditions during laparoscopic colorectal surgery	**Inclusion criteria:** Patients undergoing elective major laparoscopic colorectal surgery **Excluded:** Patients younger than 18 years, American Society of Anesthesiologists status ≥ 3, body mass index <18.5 or ≥ 35 kg/m^2, history of neuromuscular, renal or hepatic disease; previous abdominal surgery; and treatment with drugs known to affect neuromuscular function. **Number of patients:** 64 patients (32 in the deep-sugammadex group, 32 in the moderate-neostigmine group) **Mean age (SD):** 58 (12) in the deep-sugammadex group, 60 (12) in the moderate-neostigmine group	**Intervention:** Deep NMB induced by 0.6 mg/kg rocuronium, and rocuronium titrated to maintain post-tetanic count of 1 to 2. 4 mg/kg sugammadex for reversal. **Comparator:** Moderate NMB induced by 0.6 mg/kg rocuronium, and rocuronium titrated to maintain a TOF count of 1 to 2. 50 mcg/kg neostigmine with 10 mcg/kg glycopyrrolate for reversal	**Outcomes:** Time to reach TOF ratio of 0.9, dry mouth. **Follow-up:** up to 48 hours post-operatively

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Sex: 59% in the deep-sugammadex group, 63% in the moderate-neostigmine group		
Paech 2018[44] **Australia**	**Study design:** Randomized, blinded, parallel-group, active control **Setting:** Single-centre; patients recruited from hospital between September 2011 and November 2016. **Objective:** Compare the incidence of PONV associated with sugammadex and neostigmine/glycopyrrolate reversal of rocuronium-induced neuromuscular block during laparoscopic gynecological surgery.	**Inclusion criteria:** Adults (18 to 70 years), American Society of Anesthesiologists physical status 1 to 3, scheduled day-surgical laparoscopic gynecological procedure < 1 h under general anesthesia, with neuromuscular block from rocuronium **Excluded:** Need to avoid IV induction or NMB; nausea or vomiting within 48 hours before surgery; pregnancy; contraindication to any study drug; likelihood of extensive surgical procedures; and a major peri-operative change to the surgical plan or to the patient's day surgical status. **Number of patients:** 304 patients in intention-to-treat analysis (151 in sugammadex group, 153 in the neostigmine group) **Mean age (SD):** 33.7 (9.4) in sugammadex group, 33.3 (9.3) in the neostigmine group **Sex:** 100% women (due to gynecological surgery)	NMB with rocuronium (0.6 to 0.8 mg/kg) **Intervention:** 2 mg/kg sugammadex (maximum 200 mg) **Comparator:** 40 mcg/kg neostigmine (maximum 5mg) with 400 mcg glycopyrronium	**Primary outcome:** cumulative incidence of PONV in the first 6 hours post-operatively **Secondary outcomes:** PONV at 24 hours, functional aspects of recovery, including symptoms, readiness to discharge, quality of recovery **Follow-up:** up to 24 hours
Ammar 2017[41] **Egypt**	**Study design:** Randomized, double-blind controlled trial **Setting:** Patients recruited from October 2015 to June 2016. Location unclear. **Objective:** Compare between sugammadex and neostigmine concerning the recovery time from NMB in pediatric patients	**Inclusion criteria:** American Society of Anesthesiologists class I or II pediatric patients (2 to 10 years) scheduled for lower abdominal surgery **Excluded: B**ody mass index > 40 kg/m^2, kidney or liver disease, history of neuromuscular disease or malignant hyperthermia, cognitive disability, and hypersensitivity to any of the study drugs **Number of patients:** 60 patients (30 in the sugammadex group, 30 in the neostigmine group)	NMB with rocuronium (0.6 mg/kg), and maintained with 0.1 mg/kg, as needed. **Intervention:** 4 mg/kg sugammadex **Comparator:** 0.35 mg/kg neostigmine with 0.02 mg/kg atropine	**Primary outcome:** Recovery time (time from starting of sugammadex or neostigmine to reaching TOF ratio > 0.9) **Secondary outcomes:** Number of patients needed second dose of recovery agent to reach TOF ratio > 0.9, extubation time, time from reversing agent

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	undergoing lower abdominal surgeries	**Mean age (SD):** 7.8 (2.2) in the sugammadex group, 8.0 (2.4) in the neostigmine group **Sex:** 67% male in the sugammadex group, 60% male in the neostigmine group		injection to PACU arrival, PACU discharge time, residual NMB, adverse events (i.e., PONV, bradycardia, tachycardia, dry mouth, respiratory depression) **Follow-up:** post-operatively (time frame unspecified)

NMB = neuromuscular block; PACU = post-anesthesia care unit; PONV = post-operative nausea and vomiting; PostopQRS = Postoperative Quality Recovery Scale; SD = standard deviation; TOF = train-of-four

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[5]

Strengths	Limitations
Hafeez 2018[36]	
• Includes both RCTs and NRS for safety outcomes • Comprehensive list of databases searched • Study selection performed in duplicate • Provides reasons for excluding studies • Characteristics of the primary studies were well reported • Cochrane Risk of Bias tool used to assess RCTs, and Newcastle-Ottawa Scale used to assess quality of NRS • The quality of the evidence was considered in the discussion of the results	• Research question and inclusion criteria are mostly well defined, except detail is lacking with regards to the comparator group • No written protocol • Unknown how many people performed the data extraction • Did not report source of funding for included studies • One author had many competing interests, and does not report how they were managed the potential conflicts of interest
Hristovska 2017[37]	
• Well described research question and inclusion criteria • Methods established a priori in a published protocol, and deviations from the protocol were justified • Comprehensive search strategy including numerous databases, trial registries, and searching reference lists • Study selection and data extraction performed in duplicate • Large number of RCTs included • List of excluded studies provided, with justifications for exclusion • Included studies very well described • Cochrane risk of bias tool used to assess risk of bias • Sources of funding of primary studies provided • Random-effects meta-analysis model • Authors used GRADE to evaluate the quality of the evidence, and incorporated risk of bias in the assessment • Authors investigated sources of heterogeneity, such as dose • Authors declare no conflicts of interest	• Meta-analysis did not investigate the impact of the risk of bias of the individual studies on the results • Did not report the assessment of publication bias (methods indicate a funnel plot was to be performed) • Neostigmine administered alone, or with atropine or glycopyrrolate, but this was not differentiated in the analyses
Liu 2017[38]	
• Well described research question and inclusion criteria • Registered protocol, and justification for deviations from planned approach • Comprehensive search strategy including numerous databases, grey literature, and searching references lists	• Does not provide list of excluded studies • Did not report source of funding for included studies • Very high heterogeneity, even in subgroup analyses • Impact of heterogeneity on the results was not discussed • One RCT had a low risk of bias, but used a different comparator from the other studies, therefore the

Strengths	Limitations
• Study selection and data extraction performed in duplicate • Provides reasons for excluding studies • Characteristics of the primary studies were well reported • Risk of bias assed with Cochrane Risk of Bias tool and reported by individual item for each study • Publication bias was assessed with a funnel plot • Authors declare no conflicts of interest	authors could not investigate the possible impact of risk of bias on the results • Did not consider impact of risk of risk of bias or quality of the evidence in the discussion of the results • Four of nine studies were conference abstracts

GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; NRS = non-randomized study; RCT = randomized controlled trial

Table 5: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[6]

Strengths	Limitations
Alday 2019[40]	
• The objectives, patient characteristics, interventions and controls were well described • Minimal loss to follow up in both groups • Treatment groups well matched for baseline characteristics • Patients and researchers blinded to the intervention • All patients received the intervention to which they were randomized • Randomization carried out by an independent contract organization • The authors declared no conflicts of interest	• Lack of detail describing and reporting some outcomes. E.g., for residual NMB it is unclear if it is TOF or TOF ratio that is reported, affecting the interpretation of this outcome. • Nausea and vomiting listed as an outcome, but no data reported for this outcome • Actual probability (*P)* values was reported for some significant findings, but otherwise *P* values not consistently reported • More patients in the sugammadex group received an intervention during surgery (i.e., recruitment maneuver) to try re-open collapsed lungs; may affect outcome of atelectasis • Study was powered for an outcome related to lung function (not one of the outcomes of interest to this report)
Biricik 2019[42]	
• The objectives, interventions, controls, and main outcomes were well described • Patients, care providers, and research staff blinded to the intervention • Strong randomization and allocation concealment methods • All patients received the intervention to which they were randomized • No patients lost to follow-up • Actual probability (*P)* values were reported • Calculated sample size was met • The authors declared no conflicts of interest	• Limited information on baseline characteristics • Limited reporting of adverse events (unclear which adverse events were considered for reporting)
Kim 2019[43]	
• The objectives, interventions and controls were well described	• Comparator dose of neostigmine and glycopyrrolate is not based on body mass (e.g., mg/kg), rather each

Strengths	Limitations
• Treatment groups well matched for baseline characteristics • Randomization was well concealed • Patients, care providers, and research staff blinded to the intervention • All patients received the intervention to which they were randomized • No patients lost to follow-up • Calculated sample size was met • The authors declared no conflicts of interest	patient receives the same amount of the drugs (e.g., 1 mg), but sugammadex is based on body mass • Used an nonvalidated Korean translation of the main tool • Simple outcome data selectively reported for certain outcomes and time points • Unclear whether reporting results by individual items within the domains of the tool was pre-planned • Did not adjust statistical analysis for the analysis of multiple domains, individual items within domains, or three different time points • Adverse events only captured in the nociceptive domain of the tool (i.e., pain, nausea, vomiting)
Abdulatif 2018[39]	
• The objectives, interventions, controls, patients, and main outcomes were well described • Patients with liver cirrhosis and healthy controls, improves generalizability of findings • All patients received the intervention to which they were randomized • Patients blinded to intervention • No patients lost to follow up • Calculated sample size was met	• Minimal reporting of adverse events (only recurarization measured) • Probability (*P)* values were reported for significant findings, but otherwise not reported for non-significant findings • Unclear whether those measuring outcomes were blinded to the intervention (does not affect the primary outcome) • Limited detail on randomization (e.g., block size not reported) • Primary author had received an honorarium from the manufacturer of sugammadex, and does not report whether this influenced the study
Koo 2018[45]	
• The objectives, interventions, controls, patients, and main outcomes were well described • Patients, surgeons, and study investigators blinded to intervention • All patients received the intervention to which they were randomized • Minimal loss to follow-up • Actual probability (*P)* values were reported • Calculated sample size was met • The authors declared no conflicts of interest	• Study compares moderate and deep NMB, therefore not a direct comparison of the effectiveness of the reversal drugs • Minimal reporting of adverse events (did not measure pain, nausea, vomiting, residual NMB, recurarization) • Limited detail on randomization (e.g., block size not reported)
Paech 2018[44]	
• The objectives, interventions, controls, patients, and main outcomes were well described • Treatment groups well matched for baseline characteristics • Patients, care providers, data collectors, and statistician all blinded to treatment allocation • Good randomization and allocation concealment methods • Losses to follow up similar between groups, and characteristics of patients lost to follow up were described	• Four patients in the neostigmine group received sugammadex (two received the incorrect drug, two received an unblinded rescue dose). An intention-to-treat analysis was conducted. • Study findings only generalizable to women • Unclear if the analysis of the individual outcome components and time points was pre-planned or post-hoc • Statistical analysis does not adjust for the multiple outcomes and time points

Strengths	Limitations
• Actual probability (*P)* values were reported • Authors did not overstate their findings	• Calculated sample size was not met (although includes largest number of patients for the RCTs) • Minimal reporting of adverse events (did not measure residual NMB, recurarization) • Primary author received an honorarium from the manufacturer of sugammadex, and does not address whether this influenced the study
Ammar 2017[41]	
• The objectives, interventions, controls, and main outcomes were well described • Patients and study investigators were blinded from the intervention • Strong randomization and allocation concealment • All patients received the intervention to which they were randomized • No patients were lost to follow-up • Calculated sample size was met • Actual probability (*P)* values were reported • Thorough reporting of adverse events • The authors declared no conflicts of interest	• Limited to children aged 2 to 10 years • Minimal patient characteristics provided • Location of recruitment unspecified; unclear if it is single or multiple centres • Length of follow-up for adverse events unspecified

NMB = neuromuscular block; RCT = randomized controlled trial;

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Hafeez 2018[36]	
Post-operative pulmonary complications (i.e., desaturation, hypoxemia, apnea, airway manipulation, airway usage, re-intubation, CPAP, invasive mechanical ventilation): 1 RCT (unclear RoB): lower in sugammadex vs. neostigmine, *P* = 0.048 **Bradycardia**: 1 RCT (unclear RoB): lower in sugammadex vs. neostigmine, *P* = 0.04 **Post-operative abnormalities on chest radiograph** (e.g., atelectasis, pleural effusions): 1 NRS (fair quality): fewer in the sugammadex (6.9%) vs. neostigmine (16.3%), *P* = 0.015 **Need for mechanical ventilation**: 1 NRS (fair quality): no difference between sugammadex and neostigmine, *P* = 0.38	"*Postoperative pulmonary complications and bradycardia occurred less frequently in OSA patients who received sugammadex vs. neostigmine*" (p7) "*Significantly less postoperative chest radiograph changes in the OSA patients receiving sugammadex vs. neostigmine. No difference in postoperative mechanical ventilation, and hospital stay*." (p7)
Hristovska 2017[37]	
Findings analyzed for three different comparisons based on dose: 1. <u>Sugammadex 2 mg/kg vs. neostigmine 0.05 mg/kg for rocuronium reversal (main comparison)</u> **Recovery time from T2 to TOF ratio > 0.9 (for 2 mg/kg doses of sugammadex)**, minutes, mean: 1.96 sugammadex vs. 12.87 neostigmine MD = –10.22, 95% CI, –11.96 to –8.48 I^2 = 84% Number of studies: 10 RCTs Number of patients: 835 Random effects model GRADE quality of evidence = moderate 2. <u>Sugammadex 4 mg/kg vs. neostigmine 0.07 mg/kg for rocuronium reversal</u> **Recovery time from post-tetanic count 1 to 5 to TOF ratio > 0.9 (for 4 mg/kg doses of sugammadex),** minutes, mean: 2.9 sugammadex vs. 48.8 neostigmine MD = –45.78, 95% CI, –52.15 to –39.41 I^2 = 0% Number of studies: 2 RCTs Number of patients: 114 Random effects model GRADE quality of evidence = low 3. <u>Sugammadex (any dose) vs. neostigmine (any dose)</u> **Composite adverse events:**	"*Therefore, sugammadex 2 mg/kg was on average 10.22 minutes (6.6 times) faster than neostigmine 0.05 mg/kg in reversing neuromuscular blockade at T2 reappearance*" (p20) "*Sugammadex 4 mg/kg was therefore on average 45.78 minutes (16.8 times) faster than neostigmine 0.07 mg/kg in reversing neuromuscular blockade at reappearance of PTC 1 to 5*" (p21) "*Significantly fewer adverse events in the sugammadex group than in the neostigmine group*" (p22) "*In this systematic review of 41 randomized controlled trials (RCTs; 4206 participants) comparing the efficacy and safety of sugammadex versus neostigmine in reversing rocuronium-induced neuromuscular blockade (NMB), we found a large and significant difference in reversal time favoring sugammadex*." (p35) "*We found significantly fewer composite adverse events in the sugammadex group than in the neostigmine group. Specifically, the risk of composite adverse events was 283/1000 in the neostigmine group and 159/1000 in the sugammadex group. Analysis of number needed to treat for an additional beneficial outcome (NNTB) revealed that eight patients should be treated with sugammadex rather then neostigmine to avoid one patient experiencing a single random adverse event*" (p36)

Main Study Findings	Authors' Conclusion
RR = 0.60, 95% CI, 0.49 to 0.74 I^2 = 40% Number of studies: 28 RCTs (3 of which used vecuronium) Number of patients: 2298 Random effects model GRADE quality of evidence = moderate **Serious adverse events:** RR = 0.54, 95% CI, 0.13 to 2.25 I^2 = 0% Number of studies: 10 RCTs (3 of which used vecuronium) Number of patients: 959 Random effects model GRADE quality of evidence =low **PONV:** RR = 0.52, 95% CI, 0.28 to 0.97 I^2 = 0% Number of studies: 6 RCTs Number of patients: 389 Random effects model GRADE quality of evidence =low **Bradycardia:** RR = 0.16, 95% CI, 0.07 to 0.34 I^2 = 0% Number of studies: 11 RCTs Number of patients: 1218 Random effects model GRADE quality of evidence = moderate **Residual NMB:** RR = not estimable; no events in either group Number of studies: 7 RCTs Number of patients: 646 **Clinical signs of recurrence of residual NMB**: RR = 0.74, 95% CI, 0.05 to 10.74 I^2 = 33% Number of studies: 10 RCTs (8 of which reported no events) Number of patients: 1289 Total events: 1 sugammadex vs. 2 neostigmine	
Liu 2017[38]	
Primary Outcome: **Time to reversal (TOF ratio > 0.9):** WMD = –8.51, 95% CI, –11.31 to –5.71 I^2 = 98.3% Number of studies: 10 RCTs (1 low RoB (placebo controlled), 5 high RoB, 4 unclear RoB) Number of patients: 306 sugammadex, 269 control (neostigmine or placebo) GRADE quality of evidence = low	"*Our study suggests that, compared with neostigmine or a placebo, sugammadex may reverse rocuronium-induced neuromuscular blockade rapidly in pediatric patients. The included studies demonstrated that sugammadex was well tolerated in the majority of pediatric patients*" (p5) "*Further studies should be conducted to help confirm the efficacy and safety of sugammadex in this special population*." (p7)

Main Study Findings	Authors' Conclusion
Subgroup analysis by control (neostigmine only): **Time to reversal (TOF ratio > 0.9):** WMD = –7.82, 95% CI, –10.70 to –4.94 I^2 = 98.4% Number of studies: 9 RCTs (5 high RoB, 4 unclear RoB) Number of patients: 517 total GRADE quality of evidence = low **Subgroup analyses by dose of sugammadex:** **4mg/kg dose sugammadex** **Time to reversal (TOF ratio > 0.9):** WMD = –15.66, 95% CI, –23.61 to –7.70 I^2 = 97.3% Number of studies: 4 RCTs (1 low RoB (placebo controlled), 2 high RoB, 1 unclear RoB) **2mg/kg dose sugammadex** **Time to reversal (TOF ratio > 0.9):** WMD = –5.81, 95% CI, –8.50 to –3.12 I^2 = 97.0% Number of studies: 7 RCTs (1 low RoB (placebo controlled), 3 high RoB, 4 unclear RoB) <u>Secondary Outcomes – Adverse events:</u> **Bradycardia:** RR = 0.08, 95%CI, 0.01 to 0.42, *P* = 0.823 I^2 = 0% Number of studies: 5 RCTs (1 low RoB (placebo controlled), 3 high RoB, 1 unclear RoB) Number of patients: 190 sugammadex, 149 control (neostigmine or placebo) GRADE quality of evidence = low **Nausea and vomiting:** RR = 0.57, 95%CI, 0.32 to 1.03, *P* = 0.355 I^2 = 9% Number of studies: 8 RCTs (4 high RoB, 4 unclear RoB) Number of patients: 281 sugammadex, 245 control (neostigmine) GRADE quality of evidence = moderate **Bronchospasm: RR**= 0.73, 95%CI, 0.05 to 10.78, *P* = 0.216 I^2 = 34.6% Number of studies: 3 RCTs (3 high RoB, 1 unclear RoB) Number of patients: 119 sugammadex, 117 control (neostigmine) GRADE quality of evidence = very low	

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; MD = mean difference; NMB = neuromuscular block; NRS = non-randomized study; PONV = post-operative nausea and vomiting; RoB = risk of bias; RR = relative risk; WMD = weighted mean difference;

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Alday 2019[40]	
Residual NMB (TOF < 90%), immediately after extubation**:** 31% sugammadex vs. 71% neostigmine-atropine, *P* < 0.001 **Lung atelectasis**: One hour: 30% sugammadex vs. 39% neostigmine-atropine, *P* > 0.25 24 hours: 66% sugammadex vs. 74% neostigmine-atropine, *P* > 0.25 **Hypoxemia, 24 hours**: 16% sugammadex vs. 1% neostigmine-atropine, *P* = 0.013 **Pneumonia:** 1% sugammadex vs. 1% neostigmine-atropine, *P* = not reported **Additional adverse events (**reported as reasons for discontinuing spirometry study): 1 patient excluded from neostigmine-atropine group due to possible recurarization 1 patient excluded from sugammadex group due to post-operative pain	"*More than two thirds of patients in the neostigmine group and nearly one third of those in the sugammadex group had a TOF ratio B 90% immediately after extubation. Although we determined TOF ratio immediately after extubation instead of in the PACU, as commonly done, the proportion of patients with an inadequate reversal was high."* (p8) "*No difference in the incidence of atelectasis, area of atelectasis, or pulmonary complications was noted*." (p9)
Biricik 2019[42]	
Time-to-consciousness. minutes, mean (SD): 5.33 (0.88) sugammadex vs. 8.9 (0.64) neostigmine-atropine, *P* = 0.001 **Duration of wake-up test, minutes**, mean (SD): 8.5 (0.73) sugammadex vs. 14.95 (0.72) neostigmine-atropine, *P* = 0.00 **TOF score, time required from T_2 to reach T_{90}, minutes**, mean (SD): 3.1 (1.3) sugammadex vs. 4.9 (1) neostigmine-atropine, *P* = 0.001 **Complications:** Two patients in neostigmine-atropine group struggled to follow verbal commands. No other complications reported in either groups with respect to anesthesia, the wake-up test, and study drugs.	"*The main result of this study is that, in the comparison of reversal with neostigmine and atropine, return of consciousness was several (3.6) minutes faster after reversal with sugammadex; this difference cannot be exclusively explained by a faster return of neuromuscular transmission because the TOF ratio was >0.9 well before return of consciousness in both groups*." (p613) "*In the present study, the difference in times to return of consciousness seems to be a separate phenomenon to the difference in times to reversal of paralysis. That is, in both groups, the average time to consciousness was several minutes longer than the time for the TOF ratio to reach 90% (average 2.2 minutes longer in group S and 4 minutes in group N)." (p614)*
Kim 2019[43]	
Recovery rate of the physiological domain PostopQRS: 15 minutes: 95% sugammadex vs. 72% of neostigmine-glycopyrrolate, *P* = 0.020 40 minutes: no difference between groups, data shown in figure 1 day: no difference between groups, data shown in figure **Overall recovery by PostopQRS:** No difference between groups (15 and 40 minutes, 1 day), data shown in figure	"*Sugammadex was found to contribute to favorable initial postoperative recovery in the physiological domain of the PostopQRS in patients undergoing day-surgery, compared with neostigmine*." (p100)

Main Study Findings	Authors' Conclusion
Nociceptive domain of the PostopQRS: No difference between groups (15 and 40 minutes, 1 day), data shown in figure **Time-to-extubation, seconds,** median (range): 365 (330 to 434) sugammadex vs. 476.5 (420 to 519) neostigmine-glycopyrrolate, *P* < 0.001	
Abdulatif 2018[39]	
Time to recovery of TOF ratio of 0.9, minutes, mean (SD): 2.6 (1.0) normal liver-sugammadex vs. 15.7 (3.6) normal liver-neostigmine-atropine vs. 3.1 (1.0) liver cirrhosis-sugammadex vs. 14.5 (3.6) liver cirrhosis- neostigmine-atropine, *P* < 0.001 between sugammadex and neostigmine **Duration of stay in the PACU,** mean (SD): 22.8 (2.4) normal liver-sugammadex vs. 43.2 (5.0) normal liver-neostigmine-atropine vs. 23.0 (2.3) liver cirrhosis-sugammadex vs. 43.9 (7.4) liver cirrhosis- neostigmine-atropine, *P* < 0.001 between sugammadex and neostigmine **Incidence of post-operative recurarization (recurrence of NMB)**: No post-operative recurarization in any group	"*Neuromuscular block induced by rocuronium was rapidly and effectively antagonized by the administration of sugammadex in patients with Child class "A" liver cirrhosis and in controls undergoing liver resection. Sugammadex antagonism of rocuronium-induced neuromuscular block was associated with almost 80% reduction in the time to adequate neuromuscular recovery compared to neostigmine." (p934)*
Koo 2018[45]	
Time to reach TOF ratio of 0.9, minutes, mean (SD): 3.7 (1.6) deep-sugammadex vs. 7.2 (3.7) moderate-neostigmine-glycopyrrolate, *P* < 0.001 **Dry mouth,** number: 1 hour: 19 deep-sugammadex vs. 19 moderate-neostigmine-glycopyrrolate, *P* = 1.00 24 hours: 23 deep-sugammadex vs. 30 moderate-neostigmine-glycopyrrolate, *P* = 0.043 48 hours: 18 deep-sugammadex vs. 22 moderate-neostigmine-glycopyrrolate, *P* = 0.439	"*The moderate group received less rocuronium intra-operatively, but despite this, recovery to TOF 0.9 was significantly slower than that seen in the deep group*" (p1092)
Paech 2018[44]	
Cumulative incidence of PONV in the first 6 hours post-operatively: 49.0% sugammadex vs. 51.0% neostigmine-glycopyrronium, *P* = 0.951 Odds ratio = 1.08, 95% CI, 0.69 to 1.70, *P* = 0.73 **Nausea, 24 hours:** 31.7% sugammadex vs. 30.0% neostigmine-glycopyrronium, *P* = 0.765 **Vomiting, 24 hours:** 25.7% sugammadex vs. 15.0% neostigmine-glycopyrronium, *P* = 0.026 **Time to extubation**, minutes, median (range): 7 (1 to 40) sugammadex vs. 7 (1 to 160) neostigmine-glycopyrronium, *P* = 0.951	"*In this trial, sugammadex reversal of rocuronium induced non-depolarising neuromuscular block did not reduce the incidence or severity of nausea and vomiting after gynaecological laparoscopic surgery when compared with neostigmine reversal."* (p343)

Main Study Findings	Authors' Conclusion
Quality of recovery (scored 0 to 18) at 24 hours, median (range)**:** 15 (6 to 18) sugammadex vs. 15 (8 to 18) neostigmine-glycopyrronium, *P* = 0.137 **Adverse events:** Two of the women in the neostigmine group had to be given "rescue" doses of sugammadex after inadequate reversal	
Ammar 2017[41]	
Recovery time to TOF ratio > 0.9, minutes, mean (SD): 2.5 (0.8) sugammadex vs. 12.6 (4.3) neostigmine-atropine, *P* = 0.002 **Need for another dose of recovery agent**, number: 1 sugammadex vs. 8 neostigmine-atropine, *P* = 0.035 **Extubation time, minutes**, mean (SD): 2.0 (0.8) sugammadex vs. 4.3 (1.9) neostigmine-atropine, *P* = 0.005 **Time from reversing agent injection to PACU arrival, minutes**, mean (SD): 10.4 (2.9) sugammadex vs. 25.7 (6.9) neostigmine-atropine, *P* = 0.001 **PACU discharge time, minutes**, mean (SD): 42.0 (11.8) sugammadex vs. 46.6 (14.1) neostigmine-atropine, *P* = 0.115 **Residual NMB,** number: No cases in either group **PONV,** number: 1 sugammadex vs. 9 neostigmine-atropine, *P* = 0.035 **Bradycardia,** number: No cases in either group **Tachycardia,** number: 2 sugammadex vs. 11 neostigmine-atropine, *P* = 0.031 **Dry mouth,** number: 3 sugammadex vs. 22 neostigmine-atropine, *P* = 0.001 **Respiratory depression,** number: No cases in either group	"*The results of the current study have shown that sugammadex was superior over neostigmine and atropine for reversal of NMB in children as evidenced by shorter recovery and extubation times and lower incidence of adverse events*" (p377-378) "*In conclusion, sugammadex administration for reversal of rocuronium-induced NMB in pediatrics resulted in faster recovery and extubation times and lower incidence of PONV, tachycardia and dry mouth when compared with the traditional reversal by neostigmine and atropine. These advantages may be of great importance in pediatric patients undergoing outpatient surgical procedures to assure safe and rapid postoperative recovery*." (p379)

NMB – neuromuscular block; PACU = post-anesthesia care unit; PostopQRS = Postoperative Quality Recovery Scale; SD = standard deviation; TOF = train-of-four; T_2 = time to administration of the study drug; T_{90} = TOF ratio has reached 90%;

Appendix 5: Additional References of Potential Interest

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