Cochrane Library

Cochrane Database of Systematic Reviews

Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults (Review)

Hristovska AM, Duch P, Allingstrup M, Afshari A

Hristovska AM, Duch P, Allingstrup M, Afshari A.
Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults.
Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No.: CD012763.
DOI: 10.1002/14651858.CD012763.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults

Ana-Marija Hristovska[1], Patricia Duch[2], Mikkel Allingstrup[1], Arash Afshari[1]

[1]Juliane Marie Centre - Anaesthesia and Surgical Clinic Department 4013, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [2]Department of Anaesthesiology and Intensive Care Medicine, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark

Contact: Ana-Marija Hristovska, Juliane Marie Centre - Anaesthesia and Surgical Clinic Department 4013, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, Copenhagen, 2100, Denmark. anamarijahristovska@gmail.com.

Editorial group: Cochrane Anaesthesia Group.
Publication status and date: Edited (no change to conclusions), published in Issue 9, 2017.

Citation: Hristovska AM, Duch P, Allingstrup M, Afshari A. Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults. *Cochrane Database of Systematic Reviews* 2017, Issue 8. Art. No.: CD012763. DOI: 10.1002/14651858.CD012763.

ABSTRACT

Background

Acetylcholinesterase inhibitors, such as neostigmine, have traditionally been used for reversal of non-depolarizing neuromuscular blocking agents. However, these drugs have significant limitations, such as indirect mechanisms of reversal, limited and unpredictable efficacy, and undesirable autonomic responses. Sugammadex is a selective relaxant-binding agent specifically developed for rapid reversal of non-depolarizing neuromuscular blockade induced by rocuronium. Its potential clinical benefits include fast and predictable reversal of any degree of block, increased patient safety, reduced incidence of residual block on recovery, and more efficient use of healthcare resources.

Objectives

The main objective of this review was to compare the efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade caused by non-depolarizing neuromuscular agents in adults.

Search methods

We searched the following databases on 2 May 2016: Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE (WebSPIRS Ovid SP), Embase (WebSPIRS Ovid SP), and the clinical trials registries www.controlled-trials.com, clinicaltrials.gov, and www.centerwatch.com. We re-ran the search on 10 May 2017.

Selection criteria

We included randomized controlled trials (RCTs) irrespective of publication status, date of publication, blinding status, outcomes published, or language. We included adults, classified as American Society of Anesthesiologists (ASA) I to IV, who received non-depolarizing neuromuscular blocking agents for an elective in-patient or day-case surgical procedure. We included all trials comparing sugammadex versus neostigmine that reported recovery times or adverse events. We included any dose of sugammadex and neostigmine and any time point of study drug administration.

Data collection and analysis

Two review authors independently screened titles and abstracts to identify trials for eligibility, examined articles for eligibility, abstracted data, assessed the articles, and excluded obviously irrelevant reports. We resolved disagreements by discussion between review authors and further disagreements through consultation with the last review author. We assessed risk of bias in 10 methodological domains using the Cochrane risk of bias tool and examined risk of random error through trial sequential analysis. We used the principles of the GRADE

approach to prepare an overall assessment of the quality of evidence. For our primary outcomes (recovery times to train-of-four ratio (TOFR) > 0.9), we presented data as mean differences (MDs) with 95 % confidence intervals (CIs), and for our secondary outcomes (risk of adverse events and risk of serious adverse events), we calculated risk ratios (RRs) with CIs.

Main results

We included 41 studies (4206 participants) in this updated review, 38 of which were new studies. Twelve trials were eligible for meta-analysis of primary outcomes (n = 949), 28 trials were eligible for meta-analysis of secondary outcomes (n = 2298), and 10 trials (n = 1647) were ineligible for meta-analysis.

We compared sugammadex 2 mg/kg and neostigmine 0.05 mg/kg for reversal of rocuronium-induced moderate neuromuscular blockade (NMB). Sugammadex 2 mg/kg was 10.22 minutes (6.6 times) faster then neostigmine 0.05 mg/kg (1.96 vs 12.87 minutes) in reversing NMB from the second twitch (T2) to TOFR > 0.9 (MD 10.22 minutes, 95% CI 8.48 to 11.96; I^2 = 84%; 10 studies, n = 835; GRADE: moderate quality).

We compared sugammadex 4 mg/kg and neostigmine 0.07 mg/kg for reversal of rocuronium-induced deep NMB. Sugammadex 4 mg/kg was 45.78 minutes (16.8 times) faster then neostigmine 0.07 mg/kg (2.9 vs 48.8 minutes) in reversing NMB from post-tetanic count (PTC) 1 to 5 to TOFR > 0.9 (MD 45.78 minutes, 95% CI 39.41 to 52.15; I^2 = 0%; two studies, n = 114; GRADE: low quality).

For our secondary outcomes, we compared sugammadex, any dose, and neostigmine, any dose, looking at risk of adverse and serious adverse events. We found significantly fewer composite adverse events in the sugammadex group compared with the neostigmine group (RR 0.60, 95% CI 0.49 to 0.74; I^2 = 40%; 28 studies, n = 2298; GRADE: moderate quality). Risk of adverse events was 28% in the neostigmine group and 16% in the sugammadex group, resulting in a number needed to treat for an additional beneficial outcome (NNTB) of 8. When looking at specific adverse events, we noted significantly less risk of bradycardia (RR 0.16, 95% CI 0.07 to 0.34; I^2= 0%; 11 studies, n = 1218; NNTB 14; GRADE: moderate quality), postoperative nausea and vomiting (PONV) (RR 0.52, 95% CI 0.28 to 0.97; I^2 = 0%; six studies, n = 389; NNTB 16; GRADE: low quality) and overall signs of postoperative residual paralysis (RR 0.40, 95% CI 0.28 to 0.57; I^2 = 0%; 15 studies, n = 1474; NNTB 13; GRADE: moderate quality) in the sugammadex group when compared with the neostigmine group. Finally, we found no significant differences between sugammadex and neostigmine regarding risk of serious adverse events (RR 0.54, 95% CI 0.13 to 2.25; I^2= 0%; 10 studies, n = 959; GRADE: low quality).

Application of trial sequential analysis (TSA) indicates superiority of sugammadex for outcomes such as recovery time from T2 to TOFR > 0.9, adverse events, and overall signs of postoperative residual paralysis.

Authors' conclusions

Review results suggest that in comparison with neostigmine, sugammadex can more rapidly reverse rocuronium-induced neuromuscular block regardless of the depth of the block. Sugammadex 2 mg/kg is 10.22 minutes (˜ 6.6 times) faster in reversing moderate neuromuscular blockade (T2) than neostigmine 0.05 mg/kg (GRADE: moderate quality), and sugammadex 4 mg/kg is 45.78 minutes (˜ 16.8 times) faster in reversing deep neuromuscular blockade (PTC 1 to 5) than neostigmine 0.07 mg/kg (GRADE: low quality). With an NNTB of 8 to avoid an adverse event, sugammadex appears to have a better safety profile than neostigmine. Patients receiving sugammadex had 40% fewer adverse events compared with those given neostigmine. Specifically, risks of bradycardia (RR 0.16, NNTB 14; GRADE: moderate quality), PONV (RR 0.52, NNTB 16; GRADE: low quality), and overall signs of postoperative residual paralysis (RR 0.40, NNTB 13; GRADE: moderate quality) were reduced. Both sugammadex and neostigmine were associated with serious adverse events in less than 1% of patients, and data showed no differences in risk of serious adverse events between groups (RR 0.54; GRADE: low quality).

PLAIN LANGUAGE SUMMARY

Benefits and harms of sugammadex versus neostigmine in reversing induced paralysis

Background

Different levels of induced paralysis are sometimes necessary when patients are put to sleep or are prepared for operations. When the operation is finished, paralysis should be reversed in a fast, reliable, and safe way. Neostigmine is a medication that is traditionally used to reverse induced paralysis. However, its use can be associated with incomplete or slow reversal as well as changes in lung function, heart function, and vomiting and nausea. Sugammadex is a relatively new medication specifically designed to reverse rocuronium-induced paralysis in a faster, more reliable, and safer way when compared with neostigmine.

Objective

This review systematically sets out to compare the benefits and harms of sugammadex and neostigmine. The evidence is current up to May 2017.

Study characteristics

We identified 41 randomized controlled trials comparing sugammadex with neostigmine that provided suitable data on efficacy and safety. All of these trials included adults undergoing surgery and involved a total of 4206 participants.

Key results

Data indicate that sugammadex was 10.22 minutes (6.6 times) faster than neostigmine (1.96 vs 12.87 minutes) in reversing moderate induced paralysis. Sugammadex was 45.78 minutes (16.8 times) faster than neostigmine (2.9 vs 48.8 minutes) in reversing deep induced paralysis. Participants receiving sugammadex appeared to have a 40% reduced risk of experiencing harmful events than those given neostigmine. Statistically, eight persons can be treated with sugammadex as opposed to neostigmine to avoid one person experiencing a single random harmful event. The occurrence of serious harmful events was nearly non-existent and data show no differences between compared groups.

Conclusion

Sugammadex is more efficient and safer than neostigmine for reversing moderate and deep induced paralysis.

Quality of evidence

We consider our overall findings on benefits and harms to provide evidence of moderate quality in favour of sugammadex.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Sugammadex 2.0 mg/kg vs neostigmine 0.05 mg/kg

Sugammadex 2.0 mg/kg vs neostigmine 0.05 mg/kg

Patient or population: adult patients, ASA I to IV, who received non-depolarizing NMBAs
Setting: elective in-patient or day-case surgical procedures performed at centres across Europe and Asia
Intervention: sugammadex 2.0 mg/kg
Comparison: neostigmine 0.05 mg/kg

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Neostigmine 0.05 mg/kg	Sugammadex 2.0 mg/kg				
Recovery time[a] from second twitch (T2) to train-of-four ratio (TOFR) > 0.9 (moderate block)	Mean recovery time from T2 to TOFR > 0.9 was **12.87 minutes**	Mean recovery time from T2 to TOFR > 0.9 was **1.96 minutes** Mean recovery time from T2 to TOFR > 0.9 in the sugammadex group was**10.22 minutes faster** (8.48 to 11.96 minutes faster) than neostigmine	-	835 (10 studies)	⊕⊕⊕⊝[c] Moderate	TSA alfa-boundary adjusted MD is -10.22 (95% CI -12.11 to -8.33; diversity (D^2) = 87%, I^2 = 84%, random-effects model, 80% power, alpha 0.05). Cumulative Z-curve crosses the monitoring boundary (Figure 1)
Recovery time[a] from post-tetanic count (PTC) 1 to 5 to train-of-four ratio (TOFR) > 0.9 (deep block)	Outcome not clinically relevant for this comparison					
Risks of adverse events and serious adverse events[b], bradycardia, PONV, and signs of residual neuromuscular blockade	Outcome not analysed for this comparison					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)

CI: confidence interval; OR: odds ratio; RR: risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

---

[a]Recovery time was measured in minutes from administration of study drug to TOFR > 0.9 by TOF-watch assessor using acceleromyography at the same monitoring site in all studies (ulnar nerve and adductor pollicis muscle)

[b]Adverse events and serious adverse events were defined by study authors and were observed and assessed by safety outcome assessors in the operating theatre, in post-anaesthetic care unit, or up to seven days after surgery, depending on each study. Furthermore, overall clinical signs of postoperative residual paralysis reported by trials were regarded as adverse events in this review. Risk of adverse events was measured as number of adverse events per all participants and/or number of participants experiencing one or more adverse events per all participants, depending on the study. Only adverse events that were possibly, probably, or definitely related to study drug were included in risk assessments

[c]Downgraded one level owing to high risk of bias (evidence limited by inclusion of data from open-label studies and studies with potential funding bias - for details, see Figure 2 and Characteristics of included studies)

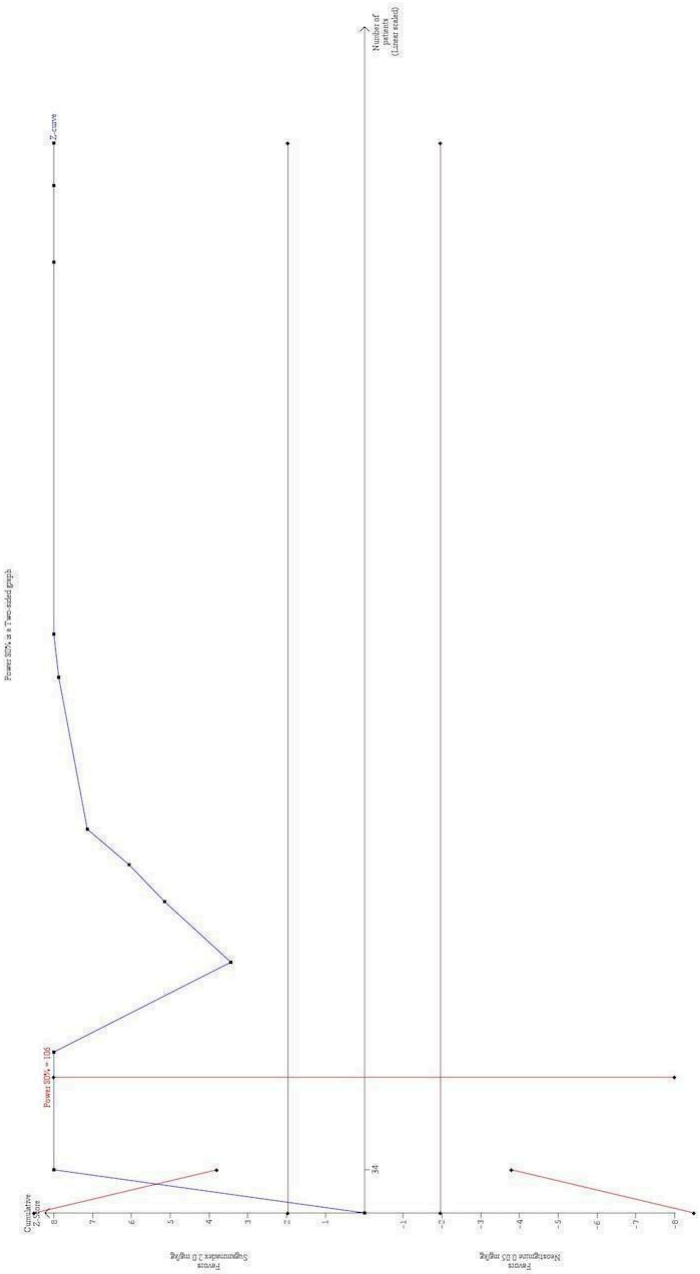


Figure 1. TSA of all trials comparing sugammadex 2.0 mg/kg vs neostigmine 0.05 mg/kg; recovery time from T2 to TOFR > 0.9 minutes. With a required information size of 106, firm evidence in place favours sugammadex in a random-effects model, with an alfa-boundary adjusted MD of -10.22 (95% CI -12.11 to -8.33; diversity (D^2) = 87%, I^2 = 84%, random-effects model). The cumulative Z-curve crosses the monitoring boundary constructed for the required information size with 80% power and alpha of 0.05. However, none of the included trials had low risk of bias, and because TSA is ideally designed for trials with low risk of bias and cannot be adjusted for risk of bias, the precision of our findings has to be downgraded. Furthermore, the degree of diversity and heterogeneity is high, which once again raises questions about the reliability of the calculated required information size.

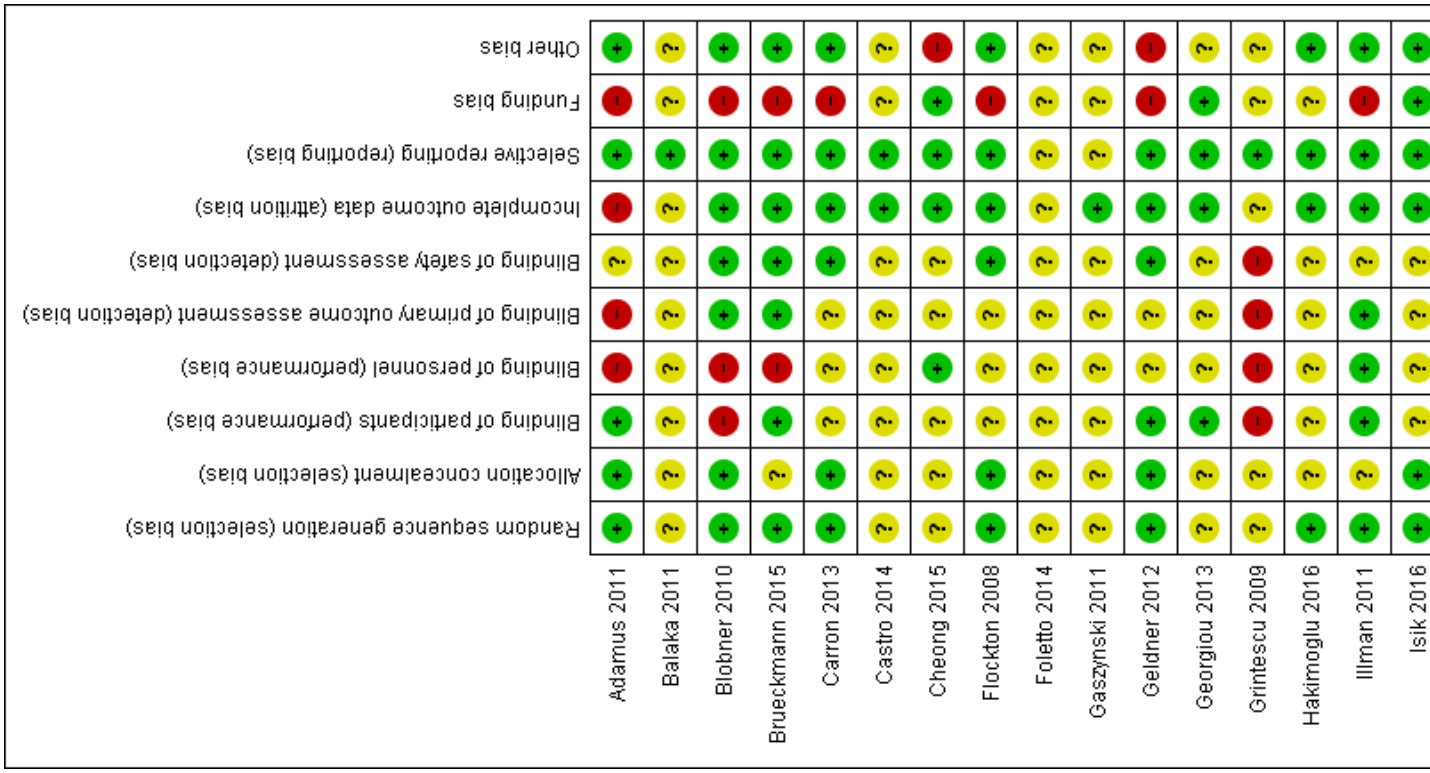


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

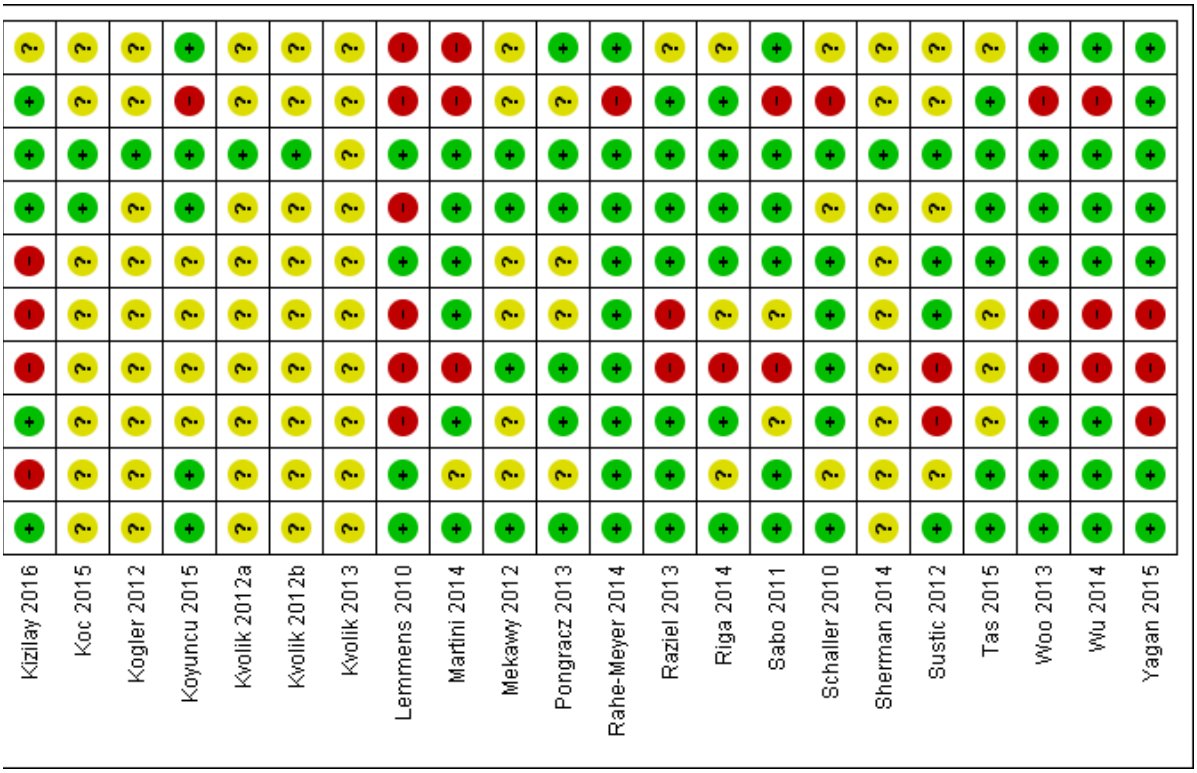


Figure 2. (Continued)

Summary of findings 2. Sugammadex 4.0 mg/kg vs neostigmine 0.07 mg/kg

Sugammadex 4.0 mg/kg vs neostigmine 0.07 mg/kg

Patient or population: adult patients, ASA I to IV, who received non-depolarizing NMBAs
Setting: elective in-patient or day-case surgical procedures performed in Italy and USA
Intervention: sugammadex 4.0 mg/kg
Comparison: neostigmine 0.07 mg/kg

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Neostigmine 0.07 mg/kg	Sugammadex 4.0 mg/kg				
Recovery time[a] from second twitch (T2) to train-of-four ratio (TOFR) > 0.9 (moderate block)	Outcome not clinically relevant for this comparison.					
Recovery time[a] from post-tetanic count (PTC 1 to 5) to train-of-four ratio (TOFR) > 0.9 (deep block)	Mean recovery time from PTC 1 to 5 to TOFR > 0.9 was **48.8 minutes**	Mean recovery time from PTC 1 to 5 to TOFR > 0.9 was **2.9 minutes** Mean recovery time from PTC 1 to 5 to TOFR > 0.9 in the sugammadex group was **45.78 minutes faster** (52.15 to 39.41 minutes faster) than in the neostigmine group	-	114 (2 studies)	⊕⊕⊖⊖[c] Low	
Risk of adverse events and serious adverse events[b], bradycardia, PONV, and signs of residual neuromuscular blockade	Outcome not analysed for this comparison					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)

CI: confidence interval; OR: odds ratio; RR: risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Recovery time was measured in minutes from administration of study drug to TOFR > 0.9 by TOF-watch assessor using acceleromyography at the same monitoring site in all studies (ulnar nerve and adductor pollicis muscle)

[b]Adverse events and serious adverse events were defined by study authors and were observed and assessed by safety outcome assessors in the operating theatre, in the post-anaesthetic care unit, or up to seven days after surgery, depending on each study. Furthermore, overall clinical signs of postoperative residual paralysis reported by trials were regarded as adverse events in this review. Risk of adverse events was measured as number of adverse events per all participants and/or number of participants experiencing one or more adverse events per all participants, depending on the study. Only adverse events that were possibly, probably, or definitely related to study drug were included in risk assessments

[c]Downgraded one level owing to high risk of bias (evidence limited by inclusion of data from open-label studies and studies with potential funding bias - for details, see Figure 2 and Characteristics of included studies) and by one level owing to imprecision (small number of participants, n = 114)

Summary of findings 3. Sugammadex (any dose) vs neostigmine (any dose)

Sugammadex (any dose) compared to Neostigmine (any dose)

Patient or population: Adult patients, ASA I-IV, who received non-depolarizing NMBAs
Setting: Elective in-patient or day-case surgical procedures performed in centres across Europe, USA and Asia
Intervention: Sugammadex (any dose)
Comparison: Neostigmine (any dose)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with neostigmine (any dose)	Risk with sugammadex (any dose)				
Recovery time[a] from second twitch (T2) to train-of-four ratio (TOFR) > 0.9 (moderate block)	Outcome not clinically relevant for this comparison					
Recovery time[a] from post-tetanic count (PTC) 1 to 5 to train-of-four ratio (TOFR) > 0.9 (deep block)	Outcome not clinically relevant for this comparison					
Risk of composite adverse events[b]	**283 per 1000**	**159 per 1000** (137 to 204)	RR 0.60 (0.49 to 0.74)	2298 (28 studies)	⊕⊕⊕⊙[c] Moderate	TSA with continuity adjustment for zero event trials (0.001 in each arm); alfa-boundary adjusted RR 0.62 (95% CI 0.51 to 0.74; diversity (D^2) = 34%, I^2 = 14%, random-effects model; 80% power, 0.05 alpha; Figure 3)

Bradycardia	84 per 1000	**13 per 1000** (6 to 28)	**RR 0.16** (0.07 to 0.34)	1218 (11 studies)	⊕⊕⊕⊖[d] Moderate	
PONV	131 per 1000	**68 per 1000** (33 to 115)	**RR 0.52** (0.28 to 0.97)	389 (6 studies)	⊕⊕⊖⊖[e] Low	
Overall signs of postoperative residual paralysis	131 per 1000	**52 per 1000** (37 to 75)	**RR 0.40** (0.28 to 0.57)	1474 (15 studies)	⊕⊕⊕⊖[f] Moderate	TSA with continuity adjustment for zero event trials (0.001 in each arm): alfa-boundary adjusted RR 0.4 (95% CI 0.27 to 0.59; diversity (D^2) = 0%, I^2 = 0%, random-effects model, 80% power, 0.05 alpha, Figure 4). Cumulative Z-curve crosses the monitoring boundary constructed for a required information size of 424 participants indicating firm evidence in favour of sugammadex
Risk of serious adverse events[b]	10 per 1000	**6 per 1000** (1 to 23)	**RR 0.54** (0.13 to 2.25)	959 (10 studies)	⊕⊕⊖⊖[g] Low	TSA with continuity adjustment for zero event trials (0.001 in each arm): alfa-boundary adjusted RR 0.35 (95% CI 0.00 to 3190; diversity (D^2) = 0%, I^2 = 0%, random-effects model, 80% power, alpha 0.05), Cumulative Z-curve does not cross the monitoring boundary constructed for a required information size of 8189 participants with 11.71% of the required information size included

*__The risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI)

CI: confidence interval; OR: odds ratio; RR: risk ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Recovery time was measured in minutes from administration of study drug to TOFR > 0.9 by TOF-watch assessor using acceleromyography at the same monitoring site in all studies (ulnar nerve and adductor pollicis muscle)

[b]Adverse events and serious adverse events were defined by study authors and were observed and assessed by safety outcome assessors in the operating theatre, in the post-anaesthetic care unit or up to seven days after surgery, depending on each study. Furthermore, overall clinical signs of postoperative residual paralysis reported by trials were regarded as adverse events in this review. Risk of adverse events was measured as number of adverse events per all participants and/or number of participants experiencing one or more adverse events per all participants, depending on the study. Only adverse events that were possibly, probably, or definitely related to study drug were included in risk assessments

[c]Downgraded one level owing to high risk of bias (evidence limited by inclusion of data from open-label studies and studies with potential funding bias - for details, see Figure 2 and Characteristics of included studies)

[d]Downgraded one level owing to high risk of bias (evidence limited by inclusion of data from open-label studies and studies with potential funding bias - for details, see Figure 2 and Characteristics of included studies)

[e]Downgraded one level owing to high risk of bias (evidence limited by inclusion of data from open-label studies and studies with potential funding bias - for details, see Figure 2 and Characteristics of included studies) and by one level owing to imprecision (small number of participants- n = 389 - and wide confidence interval (CI) - 0.28 to 0.97)

[f]Downgraded one level owing to high risk of bias (evidence limited by inclusion of data from open-label studies and studies with potential funding bias - for details, see Figure 2 and Characteristics of included studies)

[g]Downgraded one level owing to high risk of bias (evidence limited by inclusion of data from open-label studies and studies with potential funding bias - for details, see Figure 2 and Characteristics of included studies) and by one level owing to imprecision (small number of events - 10/1000 in the neostigmine group vs 6/1000 in the sugammadex group - and wide confidence interval (CI) - 0.13 to 2.25)

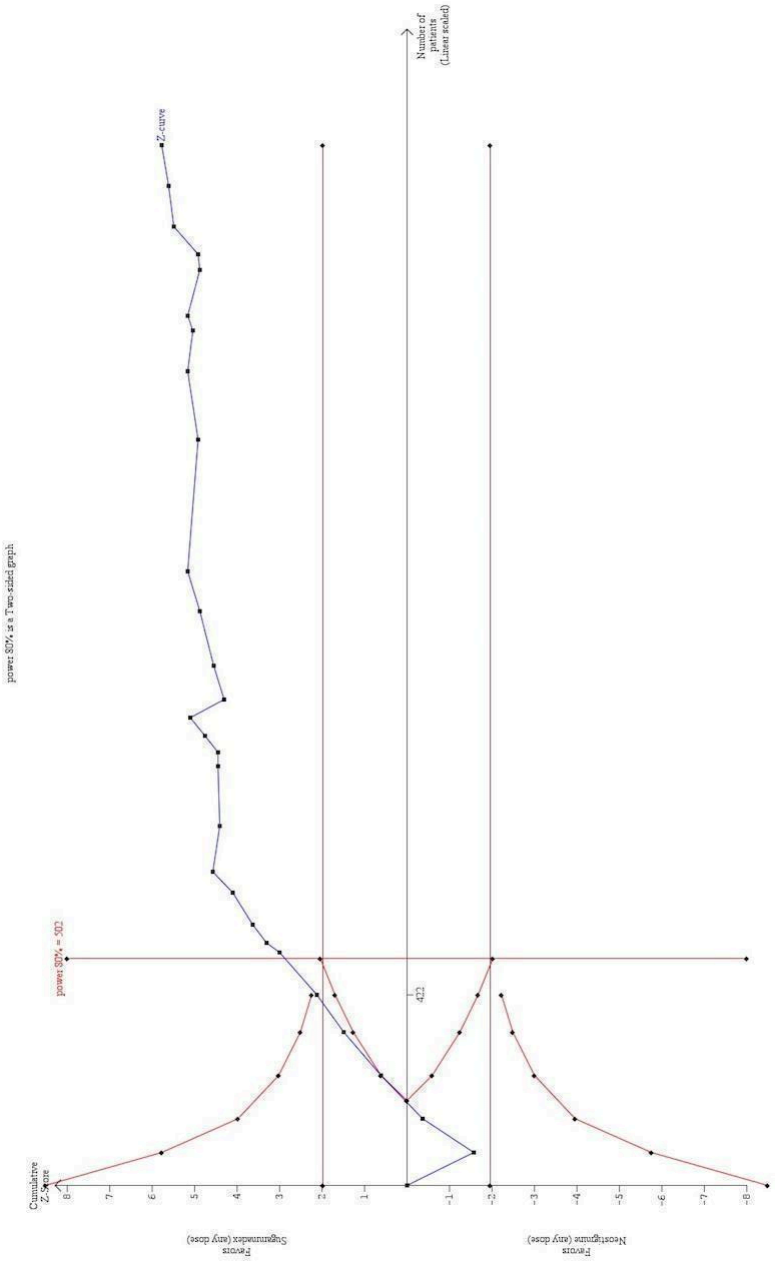


Figure 3. TSA of dichotomous data on drug-related risk of adverse events; sugammadex (any dose) vs neostigmine (any dose). This analyses includes continuity adjustment for zero event trials (0.001 in each arm) resulting in an alfa-boundary adjusted RR of 0.62 (95% CI 0.51 to 0.74; diversity (D2) = 34%, I^2 = 14%, random-effects model), with a control event proportion of 27.97%. With the required information size of 502, analyses indicated firm evidence favouring sugammadex with 2298 participants included corresponding to a relative risk reduction (RRR) of 38% with 80% power and alpha of 0.05. Despite the fact that the cumulative Z-curve does not cross the monitoring boundary directly, it is hard to imagine future trials radically changing the overall picture of this analysis. However, none of the included trials were at low risk of bias, and this does downgrade the reliability of our finding.

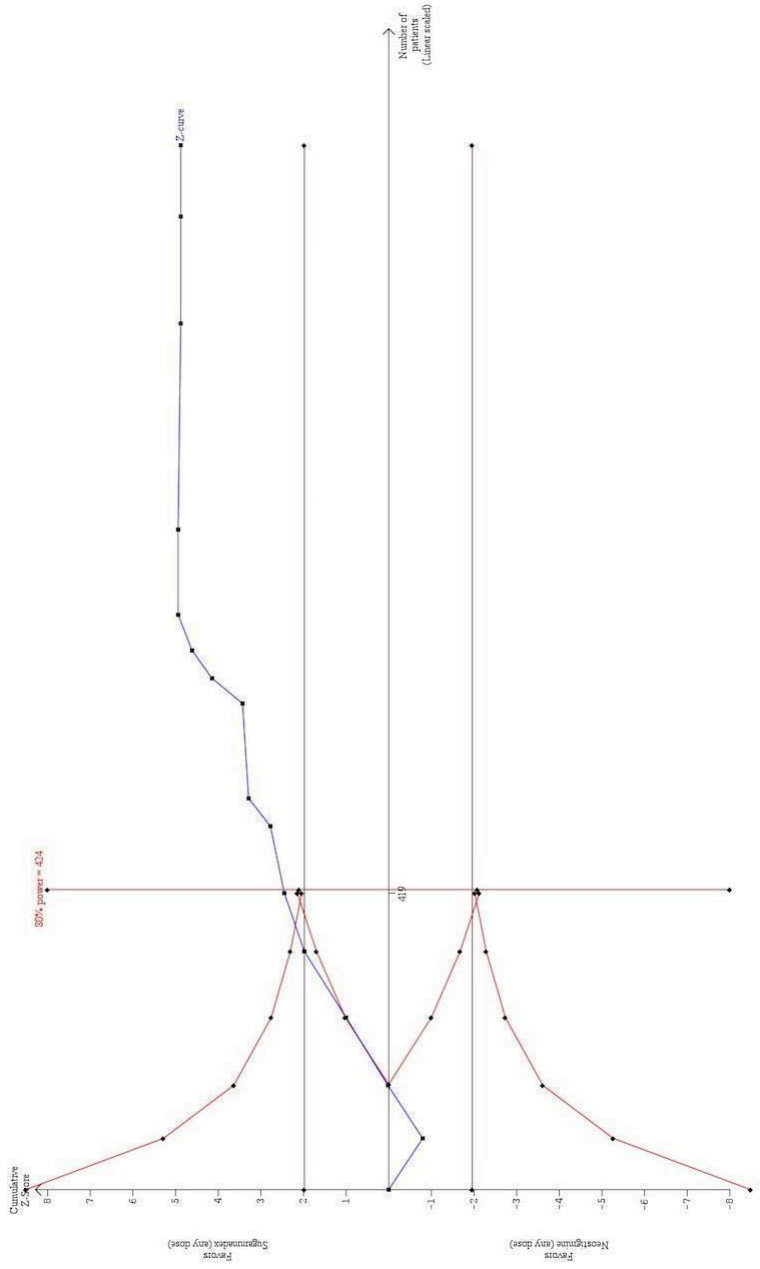


Figure 4. TSA of dichotomous data on risk of signs of residual neuromuscular blockade; sugammadex (any dose) vs neostigmine (any dose). With continuity adjustment for zero event trials (0.001 in each arm), TSA resulted in an alfa-boundary adjusted RR of 0.4 (95% CI 0.27 to 0.59; diversity (D^2) = 0%, I^2 = 0%, random-effects model, with 80% power and alpha of 0.05), with a control event proportion of 13.08%. Cumulative Z-curve crosses the monitoring boundary constructed for a required information size of 424 participants, indicating firm evidence in favour of sugammadex. However, none of the included trials had low risk of bias, and this equally diminishes the reliability and precision of our estimates.

BACKGROUND

After several discussions with the editorial team, a decision was reached to split the original review (Abrishami 2009) into two reviews based on the very extensive number of publications (> 70) identified by the updated search along with various comparators, interventions, and outcome measures.

Description of the condition

Neuromuscular blockade

Neuromuscular blocking agents (NMBAs) are drugs that induce skeletal muscle relaxation primarily by causing a decreased response to the neurotransmitter acetylcholine (ACh) at the neuromuscular junction of skeletal muscle. At that site, ACh normally produces electrical depolarization of the postjunctional membrane of the motor end-plate, which leads to conduction of muscle action potential and subsequently induces skeletal muscle contraction. Neuromuscular agents are classified as depolarizing or nondepolarizing (PubChem 2016). Non-depolarizing NMBAs may be further subdivided into aminosteroidal and curariform types of agents.

Use of NMBAs during surgery facilitates tracheal intubation, protects patients from vocal cord injury, and improves surgical conditions by suppressing voluntary or reflex skeletal muscle movements (Bowman 2006; Keating 2016). Following surgery, relaxation is no longer needed, it is important that effects of the NMBA can be quickly and effectively terminated. Postoperative residual neuromuscular blockade and resulting muscle weakness caused by non-depolarizing NMBAs have been shown to be associated with increased mortality and morbidity (Pedersen 1994; Shorten 1993). Residual neuromuscular blockade may result in pulmonary complications, for example, laboured breathing, low oxygen levels in the blood, lung infection, and entry of gastric contents into the lungs (Berg 1997; Bevan 1996; Eriksson 1993; Eriksson 1997; Murphy 2006; Murphy 2008; Sundman 2000). It can also lead to a postoperative decrease in muscle strength with associated complications, such as visual difficulties and delayed recovery and discharge time (Murphy 2011). Postoperative residual blockade frequently occurs after routine anaesthesia (Viby-Mogensen 1979). Its incidence varies among trials depending on the type of NMBA used. Some studies have demonstrated a lower incidence of residual block following short-acting or intermediate-acting NMBAs in comparison with long-acting agents (Bevan 1988; Brull 1991). However, postoperative residual neuromuscular blockade may still occur in the short-acting or intermediate-acting NMBA group, with incidence ranging from 16% to 60% (Appelbaum 2003; Baillard 2005; Bevan 1996; Debaene 2003; Fawcett 1995; Hayes 2001; Kim 2002; Maybauer 2007; McCaul 2002).

Monitoring of neuromuscular blockade

The degree of neuromuscular blockade is monitored by assessment of various patterns of electrical stimulation. The train-of-four (TOF) twitch stimulation was developed as a clinical tool that could be used to assess neuromuscular block in the anaesthetized patient (Ali 1970). This strategy involves stimulating the ulnar nerve with four supramaximal 200 microsecond stimuli separated by 0.5 seconds. This approach is repeated every 10 seconds. Twitches on a TOF pattern fade as relaxation increases. This enables the observer to compare T1 (first twitch of the TOF) versus T0 (control), as well as T4 (fourth twitch of the TOF) versus T1. This T1/T4 ratio is known as the TOF ratio (TOFR). Satisfactory recovery from neuromuscular block and clinical absence of residual curarization have not occurred until the TOFR is > 0.9 (Viby-Mogensen 2000), contrary to TOFR > 0.7, as previously suggested (Ali 1971). During profound non-depolarizing neuromuscular block, no response to TOF twitch stimulation may occur. In such circumstances, a post-tetanic count (PTC) may be useful (Viby-Mogensen 1981). If a 5 second tetanic stimulus at 50 Hz is administered, after no twitch response has been elicited, followed 3 seconds later by additional single twitches at 1 Hz, response to single twitch stimulation may occur. Although this pattern will not be seen during very profound block, a response will be seen in the early stages of recovery, before the TOF reappears. The number of post-tetanic twitches is an indication of when the first twitch of the TOF will reappear.

The muscle response to peripheral nerve stimulation can be assessed by visual and tactile methods and by electromyography, acceleromyography, and mechanomyography. Visual observation and palpation of the contracting muscle group are the easiest but least accurate methods of assessing neuromuscular block. Acceleromyography was introduced for clinical use in 1988 (Jensen 1988; Viby-Mogensen 1988). This technique measures acceleration of a distal digit, which is directly proportionate to the force of muscle contraction and therefore is inversely proportionate to the degree of neuromuscular block.

The monitor consists of an acceleration transducer (i.e. a piezo-electric ceramic wafer with an electrode on each side) and a stimulation and computing unit. The transducer can be fastened to the thumb, and when the finger is moved in response to nerve stimulation, a voltage difference develops between the two electrodes. The voltage then is measured and is registered in the computing unit.

Description of the intervention

Reversal of neuromuscular blockade

The most commonly used NMBA reversal agents are neostigmine and edrophonium, both of which are cholinesterase inhibitors. They antagonize both aminosteroidal and curariform types of non-depolarizing NMBAs by inhibiting the breakdown of ACh in the neuromuscular junction (NMJ), causing, ACh to bind the receptor and depolarize the muscle fibre and allowing greater transmission of nerve impulses. These medications, however, require that a muscarinic antagonist (e.g. glycopyrrolate, atropine) be used to compensate for their cholinergic side effects such as bradycardia, hypotension, bronchoconstriction, and postoperative nausea and vomiting (Tramer 1999). Adverse effects associated with the use of muscarinic antagonists include tachycardia, dry mouth, and urinary retention (Mirakhur 1985).

In contrast to cholinesterase inhibitors, the NMBA reversal agent sugammadex does not interfere with acetylcholinesterase receptor systems; therefore, it does not produce the muscarinic side effects associated with other reversal medications for NMBAs. Sugammadex is a synthetically modified ɣ-cyclodextrin, a chemical structure with a hydrophilic exterior and a hydrophobic core. It was specifically designed to reverse rocuronium-induced paralysis by encapsulating rocuronium; however, its inner cavity is large enough to encapsulate other aminosteroidal NMBAs such as vecuronium and, to a much lesser degree, pancuronium (Golembiewski 2016; Naguib 2009). Sugammadex does not bind nor does it reverse

the neuromuscular blocking effects of curariform NMBAs. Upon binding, it creates a complex formation between the molecule and the aminosteroidal NMBA, which results in more rapid reversal of the neuromuscular blockade than is achieved by anticholinesterase drugs (Park 2015). Sugammadex does not bind to plasma proteins and is not metabolized. It is excreted unchanged in the urine by the kidneys. Renal clearance of sugammadex is rapid - most of the dose (70%) is excreted within six hours (Golembiewski 2016).

How the intervention might work

The positively charged quaternary nitrogen of the aminosteroidal NMBA forms electrostatic bonds with negatively charged interior groups of sugammadex to encapsulate rocuronium and vecuronium (Golembiewski 2016). Sugammadex forms a stable, inactive 1:1 complex with rocuronium or vecuronium; this reduces the amount of free NMBA that is available to bind to nicotinic acetylcholine receptors at the neuromuscular junction, resulting in reversal of neuromuscular blockade (Keating 2016). Once the NMBA is removed from its site of action and is rendered inactive (by encapsulation within the sugammadex molecule in the plasma), neuromuscular transmission and muscle function are restored. By reversing aminosteroid-induced neuromuscular blockade, one can avoid the associated risks caused by residual block, can shorten time in the operating room, and can improve the patient's quality of recovery and discharge time (Arbous 2005).

Why it is important to do this review

Residual neuromuscular block is a common complication in the post-anaesthesia care unit, with approximately 40% of patients exhibiting a TOFR < 0.9 (Murphy 2010). The clinical safety and efficacy of sugammadex in reversing rocuronium-induced neuromuscular blockade have been studied in several randomized controlled trials (RCTs) that compared this medication versus placebo or conventional reversal agents (de Boer 2007; Gijsenbergh 2005; Sacan 2007; Sorgenfrei 2006; Sparr 2007). The aim of our review was to update the best available evidence on this topic and to assess the efficacy and safety of sugammadex and neostigmine in reversal of neuromuscular blockade. We aimed to systematically review RCTs conducted to examine sugammadex and neostigmine administration.

OBJECTIVES

The main objective of this review was to compare the efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade caused by non-depolarizing neuromuscular agents in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs irrespective of publication status, date of publication, blinding status, outcomes published, or language. We contacted trial investigators and study authors to ask for relevant data. We included unpublished trials only if trial data and methodological descriptions were provided in written form or could be retrieved from the trial authors. We excluded observational studies. We did not include studies using a non-standard design, such as cross-over trials and cluster-randomized trials.

Types of participants

We included adults (> 18 years of age) classified as American Society of Anesthesiologists (ASA) I to IV who had received non-depolarizing NMBAs for an elective in-patient or day-case surgical procedure, and who consented to be included in the study. We did not include paediatric participants, healthy volunteers, or participants not undergoing surgical procedures.

Types of interventions

We included all trials comparing sugammadex versus neostigmine in adults receiving non-depolarizing NMBAs. We included any dose of sugammadex and neostigmine and any time point of administration of study drug.

We excluded trials that compared sugammadex and neostigmine versus only placebo or no intervention.

Types of outcome measures

Primary outcomes

1. Recovery time from second twitch (T2) to TOFR > 0.9
2. Recovery time from post-tetanic count (PTC) 1 to 5 to TOFR > 0.9

For our first primary outcome "Recovery time from T2 to TOFR > 0.9", we compared sugammadex 2 mg/kg versus neostigmine 0.05 mg/kg. For our second primary outcome "Recovery time from PTC 1 to 5 to TOFR > 0.9", we compared sugammadex 4 mg/kg versus neostigmine 0.07 mg/kg. In all studies, the TOF-watch assessor used acceleromyography to measure recovery time in minutes from administration of the study drug to TOFR > 0.9 at the same monitoring site (ulnar nerve and adductor pollicis muscle).

Secondary outcomes

1. Risk of adverse events
2. Risk of serious adverse events

Study authors defined and safety outcome assessors observed and assessed adverse events and serious adverse events in the operating theatre, in the post-anaesthetic care unit, or up to seven days after surgery, depending on each study. Furthermore, this review regarded as adverse events overall clinical signs of postoperative residual paralysis reported by trial authors. We measured risk of adverse events as the number of adverse events per all participants and/or the number of participants experiencing one or more adverse events per all participants. We included in risk assessments only adverse events that were possibly, probably, or definitely related to study drug. We included in the analysis adverse events and serious adverse events observed following any administered dose of sugammadex and neostigmine and at any time point of study drug administration. Additionally, for the purposes of this review, we presented adverse events as specific adverse events as well as composite adverse events, defined as the combination of all adverse events.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 4); MEDLINE (WebSPIRS Ovid SP, 1950 to 2 May 2016); and Embase (WebSPIRS Ovid SP, 1980 to 2 May 2016). We applied no language restrictions. We did a top-up search in May 2017. For specific information regarding our search strategies and results, please see Appendix 1, Appendix 2, and Appendix 3.

Searching other resources

We searched for ongoing clinical trials and unpublished trials at the following Internet sites.

1. www.controlled-trials.com
2. clinicaltrials.gov
3. www.centerwatch.com

We handsearched the reference lists of reviews, randomized and non-randomized trials, and editorials for additional trials. We contacted the main authors of trials in this field to ask about missed, unreported, and ongoing trials. We applied no language restrictions to eligible reports.

We conducted the latest search on 2 May 2016, along with a top-up search in May 2017.

Data collection and analysis

Two review authors (AMH, PD) independently screened and classified all citations as potential primary studies, review articles, or other; independently examined all potentially eligible primary trials and decided on their inclusion in the review; and furthermore independently extracted data from each trial and evaluated data on methods and outcomes in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We (AMH, PD) resolved disagreements by discussion and by consultation with the last review author (AA).

Selection of studies

We assessed articles identified via the described searches and excluded obviously irrelevant reports. Two review authors (AMH, PD) independently examined articles and screened titles and abstracts to identify eligible trials. We completed this process without blinding to study authors, institutions, journals of publication, or results. We resolved disagreements by reaching consensus among two review authors (AMH, PD) and by consultation with the last review author (AA). We listed all excluded trials along with reasons for their exclusion in the Characteristics of excluded studies table.

Data extraction and management

We independently extracted and collected data from each trial without blinding to study authors, source institutions, or publication sources of trials. We resolved disagreements by discussion and approached all first authors of included trials for additional information on risks of bias. For more detailed information, please see Contributions of authors.

Assessment of risk of bias in included studies

We evaluated the validity and design characteristics of each trial. We evaluated trials for major potential sources of bias (random sequence generation, allocation concealment, blinding of participants, blinding of personnel, blinding of primary outcome assessor, blinding of secondary outcome assessor, incomplete outcome data, selective reporting, funding bias and other bias; see Appendix 4). We assessed each trial quality factor separately and defined trials as having low risk of bias only if they adequately fulfilled all of the criteria described below.

Measures of treatment effect

For our primary outcome (recovery time to TOFR > 0.9), we used mean differences (MDs) with 95% confidence intervals (CIs) because data were continuous and were measured in the same way by all trials. For our secondary outcomes (risks of adverse events and serious adverse events), we calculated risk ratios (RRs) with 95% CIs for dichotomous data (binary outcomes), which were measured in the same way between trials. We also presented data for primary and secondary outcomes as relative differences. (See Data collection and analysis section.)

Unit of analysis issues

Trials with multiple intervention groups

In accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we combined data for secondary outcomes extracted from trials with two or more groups receiving different doses of sugammadex or neostigmine. We excluded trials that compared only different doses of sugammadex or different doses of neostigmine, as well as trials without a control group.

Cross-over trials

We planned to exclude cross-over trials from our meta-analyses because of potential risk for “carry-over” of treatment effect. However, we identified no cross-over trials through our search.

Dealing with missing data

We contacted the authors of trials with missing data to retrieve relevant information. For all included trials, we noted levels of attrition and any exclusions. In cases of missing data, we chose 'complete-case analysis' for our primary outcomes, which excludes from the analysis all participants for whom the outcome is missing.

Selective outcome reporting, which occurs when non-significant results are selectively withheld from publication (Chan 2004), is defined as selection, on the basis of trial results, of a subset of the original variables recorded for inclusion in publication of trials (Hutton 2000). The most important types of selective outcome reporting include selective omission of outcomes from reports; selective choice of data for an outcome; selective reporting of different analyses using the same data; selective reporting of subsets of the data; and selective underreporting of data (Higgins 2011).

Assessment of heterogeneity

We explored heterogeneity using the I^2 statistic and the Chi^2 test. An I^2 statistic above 50% represents substantial heterogeneity (Higgins 2011). In cases of substantial heterogeneity, we tried to determine the cause of heterogeneity by performing relevant subgroup and sensitivity analyses (excluding potential outliers to see visual impact of the overall value of the I^2 statistic on forest plots). We used the Chi^2 test to provide an indication of heterogeneity between

trials, with a P value ≤ 0.1 considered significant. However, in cases of presumed substantial clinical heterogeneity within an analysis, we planned to use the random-effects model independent of I^2 value.

Assessment of reporting biases

We included both published and unpublished studies during the selection process. We attempted to source published protocols for each of our included studies by using clinical trials registers. We compared published protocols versus published study results to assess the risk of selective reporting bias. Two review authors (AMH and PD) resolved disagreements by discussion and by consultation with the last review author (AA). As we included a sufficient number of studies (greater than 10), we assessed reporting biases (such as publication bias) by using funnel plots. We used the asymmetry of the funnel plot to assess risk of publication and other reporting bias (Higgins 2011). An asymmetrical funnel plot may indicate publication of only positive results (Egger 1997).

Data synthesis

Data analysis

We used Review Manager software (RevMan 5.3.5) and calculated MDs with 95% CIs for continuous outcomes, and RRs with 95% CIs for dichotomous variables. We used the Chi^2 test to obtain an indication of heterogeneity between trials, with P ≤ 0.1 considered significant. We quantified the degree of heterogeneity observed in the results by using the I^2 statistic, which can be interpreted as the proportion of total variation observed between trials that is attributable to differences between trials rather than to sampling error (Higgins 2011). I^2 > 75% is considered as very heterogeneous. However, we chose a random-effects model for all of our analyses because clinical heterogeneity was a considerable issue beside the inter-study heterogeneity expressed by the I^2 statistic. Thus, we saw little rationale to carry out comparative analyses examining the impact of the choice between using a fixed-effect versus a random-effects model.

Trial sequential analysis

Risk of type 1 errors in meta-analyses due to sparse data and repeated significance testing following updates with new trials remains a serious concern (Brok 2009; Thorlund 2009; Wetterslev 2008; Wetterslev 2009). As a result, spurious P values due to systematic errors from trials with high risk of bias, outcome reporting bias, publication bias, early stopping for benefit, and small trial bias may result in false conclusions. In a single trial, interim analysis increases the risk of type 1 errors. To avoid type 1 errors, group sequential monitoring boundaries (Lan 1983) are used to decide whether a trial could be terminated early because of a sufficiently small P value, with the cumulative Z-curve crossing the monitoring boundary.

Sequential monitoring boundaries can be applied equally to meta-analyses and are labelled 'trial sequential monitoring boundaries'. In 'trial sequential analysis' (TSA), the addition of each new trial to a cumulative meta-analysis is viewed as an interim meta-analysis, which provides useful information on the need for additional trials (Wetterslev 2008).

It is appropriate and wise to adjust new meta-analyses for multiple testing on accumulating data to control overall type 1 error risk in cumulative meta-analysis (Pogue 1997; Pogue 1998; Thorlund 2009; Wetterslev 2009).

When TSA is performed, the cumulative Z-curve crossing the boundary indicates that a sufficient level of evidence has been reached; as a consequence, one may conclude that no additional trials may be needed. However, evidence is insufficient to allow a conclusion if the Z-curve does not cross the boundary or does not surpass the required information size.

To construct trial sequential monitoring boundaries (TSMBs), one needs a required information size, which is calculated as the least number of participants required in a well-powered single trial with low risk of bias (Brok 2009; Pogue 1998; Wetterslev 2008).

In this updated review, we adjusted the required information size for heterogeneity by using the diversity adjustment factor (Wetterslev 2009). We applied TSA, as it prevents an increase in the risk of type 1 errors (20%). If the actual accrued information size was too small, we provided the required information size in the light of actual diversity (Wetterslev 2009).

Subgroup analysis and investigation of heterogeneity

We conducted the following subgroup analyses.

1. Sugammadex 2.0 mg/kg versus neostigmine 0.05 mg/kg: recovery time from T2 to TOFR > 0.9
   a. Total intravenous anaesthesia (TIVA) versus volatile anaesthetics
2. Sugammadex, any dose, versus neostigmine, any dose: adverse events
   a. Composite adverse events: different dosages of sugammadex versus neostigmine
   b. Composite adverse events: TIVA versus volatile anaesthetics
   c. Bradycardia: atropine versus glycopyrrolate
   d. Postoperative nausea and vomiting (PONV): TIVA versus volatile anaesthetics

If analyses of various subgroups were significant, we planned to perform a test of interaction (Altman 2003). We considered P values < 0.05 as indicating significant interaction between treatments and subgroup categories. However, because subgroup analyses showed no significant differences, we performed no tests of interaction.

Sensitivity analysis

We conducted the following sensitivity analyses.

1. Sugammadex 2.0 mg/kg versus neostigmine 0.05 mg/kg, recovery time from T2 to TOFR > 0.9, excluding meeting abstracts
2. Sugammadex, any dose, versus neostigmine, any dose, composite adverse events, excluding meeting abstracts

Summary of findings table and GRADE

We used the principles of the GRADE approach to perform an overall assessment of evidence related to all of our outcomes. We constructed a 'Summary of findings' table using GradePro software. As outcomes of clinical interest, we chose to present recovery time from T2 to TOFR > 0.9 (moderate block); recovery time from PTC 1 to 5 to TOFR > 0.9 (deep block); risks of adverse events, serious adverse events, bradycardia, and PONV; and signs of residual

neuromuscular blockade (see Summary of findings for the main comparison; Summary of findings 2; and Summary of findings 3).

RESULTS

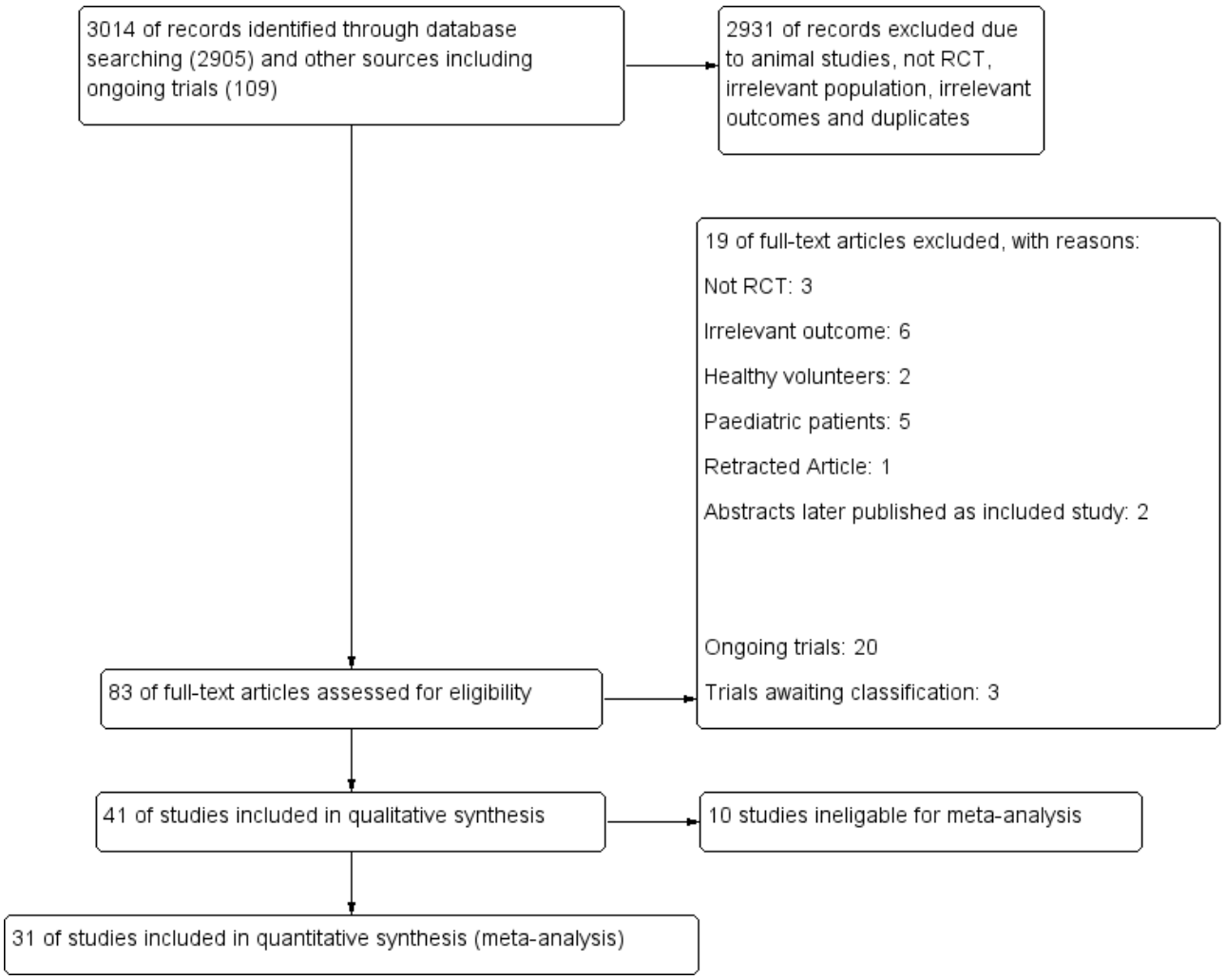
Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; and Characteristics of ongoing studies.

Results of the search

In May 2016, through electronic searches and searches of the references of potentially relevant articles, we identified 2502 publications. We excluded 2431 publications, as they were duplicates (n = 675), measured clearly irrelevant outcomes, or were not RCTs. We retrieved a total of 72 relevant publications for further assessment. Of these, 14 were ongoing trials, one trial was awaiting classification, and 16 were excluded with reasons. We reran the search in May 2017 and identified 513 citations (503 by searching databases and 10 by searching clinical trials). Upon reading titles/excluding duplicates, we found 11 studies of interest; of these, two are awaiting classification, six are ongoing, and three were excluded with explanation. In total, 41 RCTs (N = 4206) met our inclusion criteria. Of these, 31 trials (N = 2559) were eligible for meta-analyses, 20 are ongoing, and three are awaiting classification. We have provided search results in a flow chart in Figure 5.

Figure 5. Study flow diagram.



Included studies

We included 41 trials (4206 participants) in our review.

Publication type

Of the 41 included trials, 29 (71%) were published as full-text papers (Adamus 2011; Blobner 2010; Brueckmann 2015; Carron 2013; Castro 2014; Cheong 2015; Flockton 2008; Gaszynski 2011; Geldner 2012; Hakimoglu 2016; Illman 2011; Isik 2016; Jones 2008; Kaufhold 2016; Khuenl-Brady 2010; Kizilay 2016; Koc 2015; Koyuncu 2015; Lemmens 2010; Martini 2014; Mekawy 2012; Pongracz 2013; Rahe-Meyer 2014; Sabo 2011; Schaller 2010; Tas 2015; Woo 2013; Wu 2014; Yagan 2015). Twelve (29%) of the 41 trials were available only as meeting abstracts (Balaka 2011; Foletto 2014; Georgiou 2013; Grintescu 2009; Kogler 2012; Kvolik 2012a; Kvolik 2012b; Kvolik 2013; Raziel 2013; Riga 2014; Sherman 2014; Sustic 2012). All of the

included trials were published in English, with the exception of one article that was published in Turkish (Koc 2015). We contacted all 41 trial authors for missing information; 12 (29%) replied and provided supplementary data.

Participants and settings

We reported full details of participants and settings in the Characteristics of included studies section.

Of the 41 included studies, 30 were single-centre studies conducted in 15 countries: Turkey (seven studies: Hakimoglu 2016, Isik 2016, Kizilay 2016, Koc 2015, Koyuncu 2015, Tas 2015, Yagan 2015), Croatia (five studies: Kogler 2012, Kvolik 2012a, Kvolik 2012b, Kvolik 2013, Sustic 2012), Greece (three studies: Balaka 2011, Georgiou 2013, Riga 2014), Germany (two studies: Kaufhold 2016, Schaller 2010), Israel (two studies: Raziel 2013, Sherman 2014), Italy (two studies: Carron 2013, Foletto 2014) and one study each in Egypt (Mekawy 2012), Hungary (Pongracz 2013), Netherlands (Martini 2014), Czech Republic (Adamus 2011), Portugal (Castro 2014), Poland (Gaszynski 2011), Romania (Grintescu 2009), Korea (Cheong 2015), and USA (Brueckmann 2015). Eleven were multiple-centre studies: 22 European centres in Rahe-Meyer 2014, 13 European centres in Blobner 2010 and Khuenl-Brady 2010, 10 European centres in Geldner 2012, nine US centres in Jones 2008 and Lemmens 2010, eight European centres in Flockton 2008, seven Korean centres in Woo 2013, six Chinese plus four European centres in Wu 2014, two Finnish centres in Illman 2011, and an unspecified number of US centres in Sabo 2011.

The sample size of included trials ranged from 22 to 1198 adults (aged > 18 years) with ASA status I to IV. Among studies reporting ASA status, the distribution of participants across groups was as follows: ASA I: 1003 participants (32%); ASA II: 1772 participants (56%); ASA III: 331 participants (11%); and ASA IV: 31 participants (1%).

Five trials included only morbidly obese (MOB) participants (Carron 2013; Castro 2014; Foletto 2014; Gaszynski 2011; Raziel 2013), and one trial focused on super-obese (SO) patients (Georgiou 2013). One trial included participants classified as New York Heart Association (NYHA) II to III (Kizilay 2016), and one trial investigated participants with myasthenia gravis (Balaka 2011).

Participants underwent diverse elective surgical procedures under general anaesthesia: extreme lateral interbody fusion (Adamus 2011); trans-sternal thymectomy (Balaka 2011); laparoscopic or open abdominal surgery (Brueckmann 2015); laparoscopic removal of adjustable gastric banding (Carron 2013); laparoscopic bariatric surgery (Castro 2014); laparoscopic sleeve gastrectomy (Foletto 2014; Raziel 2013; Sherman 2014); elective bariatric surgery (Gaszynski 2011); laparoscopic cholecystectomy or appendectomy (Geldner 2012); laparoscopic cholecystectomy (Grintescu 2009; Sustic 2012); open bariatric surgery (Georgiou 2013); arthroscopic surgery (Hakimoglu 2016); non-cardiac surgery (Kizilay 2016); interventional bronchoscopy (Kogler 2012); extremity surgery (Koyuncu 2015); thyroidectomy (Kvolik 2012a; Kvolik 2012b); thyroidectomy or breast cancer surgery (Kvolik 2013); laparoscopic prostatectomy or nephrectomy (Martini 2014); endoscopic sinus surgery with or without septoplasty (Mekawy 2012); hip or knee joint replacement or hip fracture surgery (Rahe-Meyer 2014); open abdominal and urogenital surgery (Sabo 2011); and septoplasty (Tas 2015).

Four studies combined participants who underwent diverse elective surgical procedures (Blobner 2010; Cheong 2015; Lemmens 2010; Woo 2013). Twelve studies provided no data on the type of elective surgical procedure performed (Flockton 2008; Illman 2011; Isik 2016; Jones 2008; Kaufhold 2016; Khuenl-Brady 2010; Koc 2015; Pongracz 2013; Riga 2014; Schaller 2010; Wu 2014; Yagan 2015).

Investigators maintained anaesthesia with opioid most often in combination with volatile anaesthetics, specifically with sevoflurane in 15 trials (Adamus 2011; Blobner 2010; Cheong 2015; Grintescu 2009; Jones 2008; Khuenl-Brady 2010; Kizilay 2016; Koc 2015; Lemmens 2010; Pongracz 2013; Riga 2014; Sabo 2011; Tas 2015; Woo 2013; Yagan 2015); desflurane in six trials (Carron 2013; Castro 2014; Gaszynski 2011; Hakimoglu 2016; Isik 2016; Koyuncu 2015); isoflurane in one trial (Mekawy 2012); and sevoflurane or desflurane in one trial (Illman 2011). Twelve trials used propofol for maintenance (Flockton 2008; Foletto 2014; Geldner 2012; Georgiou 2013; Kaufhold 2016; Kogler 2012; Kvolik 2012a; Kvolik 2012b; Kvolik 2013; Martini 2014; Schaller 2010; Wu 2014); and two trials used any anaesthetic, according to usual practice (Brueckmann 2015; Rahe-Meyer 2014). Four trials provided no information on anaesthesia maintenance (Balaka 2011; Raziel 2013; Sherman 2014; Sustic 2012).

Most trials used rocuronium as a non-depolarizing neuromuscular blocking-agent (NMBA). However, Lemmens 2010 used vecuronium; Rahe-Meyer 2014 used rocuronium or vecuronium, according to usual practice at the site; Flockton 2008 compared sugammadex following rocuronium versus neostigmine following cisatracurium; and Martini 2014 compared atracurium for induction and mivacurium for maintenance versus rocuronium for both induction and maintenance. Two studies provided no information on the NMBA agent used (Castro 2014; Sherman 2014).

Interventions

We summarized the interventions reported in included studies under Characteristics of included studies.

All studies compared sugammadex and neostigmine, but investigators administered these drugs in different doses: Adamus 2011 and Sustic 2012 compared sugammadex 2 mg/kg versus neostigmine 0.04 mg/kg; and 15 trials compared sugammadex 2 mg/kg versus neostigmine 0.05 mg/kg (Blobner 2010; Castro 2014; Cheong 2015; Flockton 2008; Foletto 2014, Grintescu 2009, Illman 2011; Kvolik 2012a, Kvolik 2012b, Khuenl-Brady 2010; Koc 2015; Tas 2015; Woo 2013; Wu 2014; Yagan 2015). Two trials compared sugammadex 2 mg/kg versus neostigmine 0.07 mg/kg (Kogler 2012; Koyuncu 2015).

Three studies compared sugammadex 2 mg/kg versus neostigmine 2.5 mg (Balaka 2011; Raziel 2013; Sherman 2014). Kizilay 2016 compared sugammadex 3 mg/kg versus neostigmine 0.03 mg/kg, Isik 2016 compared sugammadex 4 mg/kg versus neostigmine 0.04 mg/kg. Four trials compared sugammadex 4 mg/kg versus neostigmine 0.05 mg/kg (Geldner 2012; Hakimoglu 2016; Mekawy 2012; Sabo 2011). Three trials compared sugammadex 4 mg/kg versus neostigmine 0.07 mg/kg (Carron 2013; Jones 2008; Lemmens 2010). Rahe-Meyer 2014 compared sugammadex 4 mg/kg versus usual care (neostigmine with glycopyrrolate or atropine, no dose specified, or placebo/spontaneous recovery). Martini 2014 compared sugammadex 4 mg/kg versus neostigmine 1 to 2 mg, and Riga 2014 did not specify dose for sugammadex

or neostigmine. Four trials compared several different doses of sugammadex versus several different doses of neostigmine (Brueckmann 2015; Kaufhold 2016; Pongracz 2013; Schaller 2010). Georgiou 2013 compared sugammadex 2 mg/kg ideal body weight versus sugammadex 2 mg/kg corrected body weight versus neostigmine 50 µg/kg ideal body weight versus neostigmine 50 µg/kg corrected body weight, Carron 2013 compared sugammadex 4 mg/kg total body weight versus neostigmine 70 µg/kg lean body weight, and Gaszynski 2011 compared sugammadex 2 mg/kg corrected body weight versus neostigmine 50 µg/kg corrected body weight.

Outcomes

Of the 41 RCTs that met our inclusion criteria, 12 trials (n = 949) were eligible for meta-analysis of the primary outcome (recovery time > TOFR 0.9) (Blobner 2010; Carron 2013; Cheong 2015; Foletto 2014; Gaszynski 2011; Georgiou 2013; Grintescu 2009; Illman 2011; Jones 2008; Koc 2015; Woo 2013; Wu 2014).

Of the 41 trials, 28 (N = 2298) were eligible for meta-analysis of secondary outcomes (adverse events and serious adverse events): Adamus 2011; Balaka 2011; Blobner 2010; Brueckmann 2015; Carron 2013; Castro 2014; Cheong 2015; Flockton 2008; Gaszynski 2011; Geldner 2012; Hakimoglu 2016; Illman 2011; Jones 2008; Kaufhold 2016; Khuenl-Brady 2010; Kizilay 2016; Koc 2015; Kogler 2012; Koyuncu 2015; Kvolik 2012a; Lemmens 2010; Mekawy 2012; Pongracz 2013; Sabo 2011; Schaller 2010; Woo 2013; Wu 2014; Yagan 2015).

Ten RCTs (N = 1647) were ineligible for meta-analysis (Isik 2016; Kvolik 2012a; Kvolik 2013; Martini 2014; Rahe-Meyer 2014; Raziel 2013; Riga 2014; Sherman 2014; Sustic 2012; Tas 2015) for the reasons provided in Table 1 (table of studies ineligible for meta-analysis).

See Characteristics of included studies for further information on the included studies.

Excluded studies

Among 83 identified relevant trials, we excluded 19 publications (Aho 2012; Baysal 2013; Dahaba 2012; Gaona 2012; Ghoneim 2015; Harazim 2014; Kakinuma 2013; Kara 2014; Kzlay 2013; Nagy 2014; Ozgun 2014; Pecek 2013; Sacan 2007; Schepens 2015; Stourac 2016; Veiga Ruiz 2011; Nagashima 2016; Nemes 2016; NCT03111121).

We have explained reasons for exclusion of each trial in the Characteristics of excluded studies table.

Ongoing studies

We identified 20 ongoing and unpublished trials by searching www.controlled-trials.com, clinicaltrials.gov, and www.centerwatch.com. The following five trials have been completed but to the best of our knowledge, no data from these trials have yet been published: NCT01539044; NCT01748643; NCT02160223; NCT02330172; NCT02414880). Six trials are currently recruiting participants (NCT02256280; NCT02361060; NCT02454504; NCT02666014; NCT02698969; NCT02860507). Six trials are classified as ongoing (NCT02909439; NCT02697929; NCT03108989; NCT03116997; NCT02939430; NCT03144453) and three trials are not yet open for recruiting participants (NCT02648503; NCT02845375; NCT02861131).

See Characteristics of ongoing studies for details.

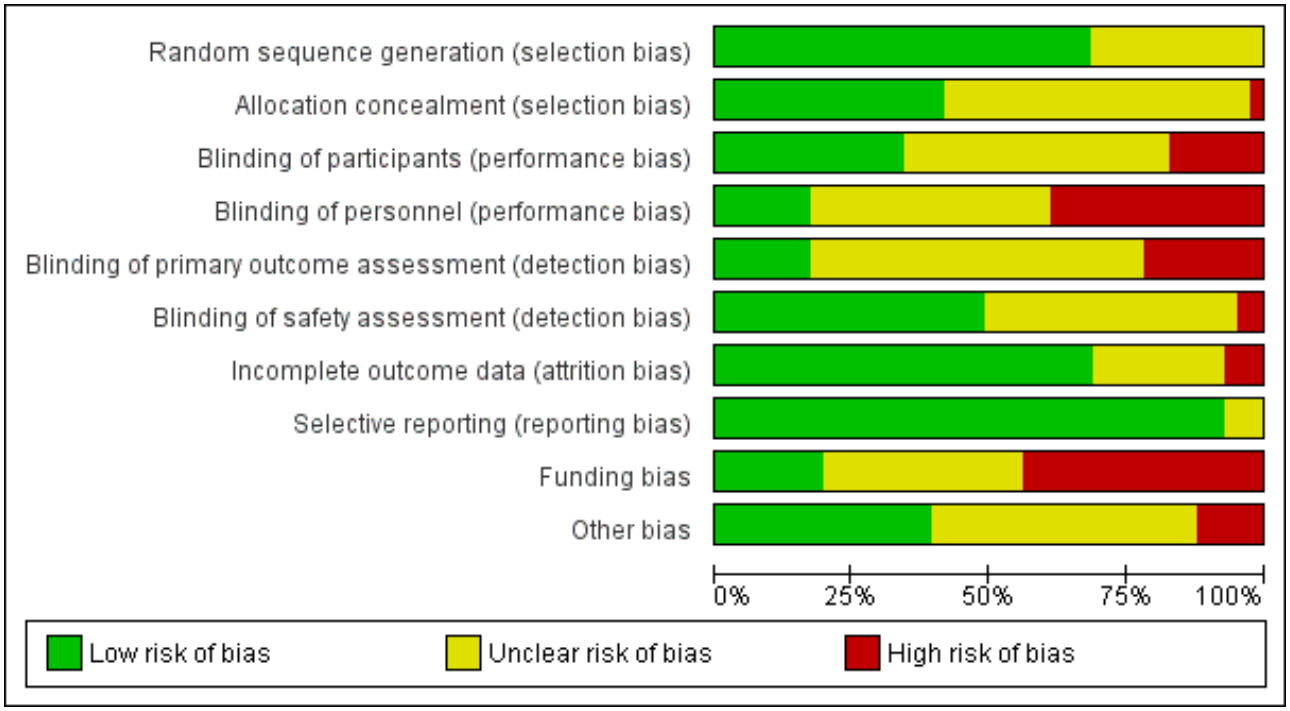
Studies awaiting classification

We reran the search in May 2017 and found three trials (NCT02243943; Kim 2016; Sen 2016) that published data after we had completed our main search in May 2016; we will include these trials in the next updated version of this review.

Risk of bias in included studies

We assessed the risk of bias of included studies using the 'Risk of bias' tool developed by Cochrane. The first review author (AMH) and the second review author (PD) independently assessed risk of bias for each study and resolved disagreements by discussion or by consultation with the last review author (AA). We have presented the various bias domains in Figure 2 - Risk of bias graph - and Figure 6 - Risk of bias summary

Figure 6. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation (selection bias)

Twenty-seven trials (66%) reported adequate generation of random sequence that was computer-based (Adamus 2011; Brueckmann 2015; Carron 2013; Hakimoglu 2016; Illman 2011; Isik 2016; Jones 2008; Kaufhold 2016; Martini 2014; Mekawy 2012; Pongracz 2013; Raziel 2013; Riga 2014; Schaller 2010; Sustic 2012; Tas 2015; Yagan 2015); or was performed by using a central randomization system (Blobner 2010; Flockton 2008; Geldner 2012; Khuenl-Brady 2010; Koyuncu 2015; Lemmens 2010; Rahe-Meyer 2014; Sabo 2011; Woo 2013; Wu 2014).

Furthermore, one trial (2%) reported randomization by lots (Kizilay 2016). Thirteen trials (32%) did not report sufficient information for assessment of risk of bias(Balaka 2011; Castro 2014; Cheong 2015; Foletto 2014; Gaszynski 2011; Georgiou 2013; Grintescu 2009; Koc 2015; Kogler 2012; Kvolik 2012a; Kvolik 2012b; Kvolik 2013; Sherman 2014).

Allocation concealment (selection bias)

Eighteen trials (44%) reported adequate allocation concealment performed by using sequentially numbered opaque sealed envelopes (SNORES) (Adamus 2011; Carron 2013; Isik 2016; Jones 2008; Martini 2014; Tas 2015; Yagan 2015); or secondary to a central randomization system (Blobner 2010; Flockton 2008; Geldner 2012; Khuenl-Brady 2010; Koyuncu 2015; Lemmens 2010; Rahe-Meyer 2014; Raziel 2013; Sabo 2011; Woo 2013; Wu 2014).

One trial (2%) reported using no allocation concealment (Kizilay 2016). Twenty-two trials (54%) did not describe their method of allocation concealment (Balaka 2011; Brueckmann 2015; Castro 2014; Cheong 2015; Foletto 2014; Gaszynski 2011; Georgiou 2013; Grintescu 2009; Hakimoglu 2016; Illman 2011; Kaufhold 2016; Koc 2015; Kogler 2012; Kvolik 2012a; Kvolik 2012b; Kvolik 2013; Mekawy 2012; Pongracz 2013; Riga 2014; Schaller 2010; Sherman 2014; Sustic 2012).

Blinding

Blinding of participants (performance bias)

Fourteen trials (34%) adequately blinded participants and therefore had low risk of performance bias (Adamus 2011; Brueckmann 2015; Geldner 2012; Georgiou 2013; Illman 2011; Kizilay 2016; Martini 2014; Pongracz 2013; Rahe-Meyer 2014; Raziel 2013; Riga 2014; Schaller 2010; Woo 2013; Wu 2014).

Eight trials (20%) did not adequately blind participants and therefore had high risk of performance bias; two of these specifically reported that participants were not blinded (Sustic 2012; Yagan 2015), and six were marked as “open-label” trials (Blobner 2010; Flockton 2008; Grintescu 2009; Jones 2008; Khuenl-Brady 2010; Lemmens 2010).

The remaining 19 trials (46%) did not provide sufficient data on participant blinding and we assigned risk of performance bias as unclear(Balaka 2011; Carron 2013; Castro 2014; Cheong 2015; Foletto 2014; Gaszynski 2011; Hakimoglu 2016; Isik 2016; Kaufhold 2016; Koc 2015; Kogler 2012; Koyuncu 2015; Kvolik 2012a; Kvolik 2012b; Kvolik 2013; Mekawy 2012; Sabo 2011; Sherman 2014; Tas 2015).

Blinding of personnel (performance bias)

Seven trials (17%) reported adequate blinding of the anaesthesiologist and therefore had low risk of performance bias (Cheong 2015; Illman 2011; Kaufhold 2016; Mekawy 2012; Pongracz 2013; Rahe-Meyer 2014; Schaller 2010).

Seventeen trials (41%) did not report adequate blinding of anaesthesiologists and therefore had high risk of performance bias; 11 of these specifically reported that the anaesthesiologist was not blinded: (Adamus 2011; Brueckmann 2015; Kizilay 2016; Martini 2014; Raziel 2013; Riga 2014; Sabo 2011; Sustic 2012; Woo 2013; Wu 2014; Yagan 2015), and six trials were marked as "open-label" trials (Blobner 2010; Flockton 2008; Grintescu 2009; Jones 2008; Khuenl-Brady 2010; Lemmens 2010).

The remaining 17 trials (41%) did not provide sufficient data on anaesthesiologist blinding and therefore had unclear risk of performance bias (Balaka 2011; Carron 2013; Castro 2014; Foletto 2014; Gaszynski 2011; Geldner 2012; Georgiou 2013; Hakimoglu 2016; Isik 2016; Koc 2015; Kogler 2012; Koyuncu 2015; Kvolik 2012a; Kvolik 2012b; Kvolik 2013; Sherman 2014; Tas 2015).

Blinding of TOF-watch assessment (detection bias)

Two trials (5%) specifically reported that the anaesthesiologist was also the TOF-watch assessor: (Adamus 2011; Illman 2011). Four trials (10%) reported adequate blinding of the TOF-watch assessor and therefore had low risk of performance bias (Brueckmann 2015; Illman 2011; Martini 2014; Schaller 2010).

Twelve trials (29%) did not provide adequate blinding of the TOF-watch assessor and therefore had high risk of detection bias; six of these trials specifically reported that the anaesthesiologist was not blinded (Adamus 2011; Kizilay 2016; Raziel 2013; Woo 2013; Wu 2014; Yagan 2015), and six trials were marked as "open-label" trials (Blobner 2010; Flockton 2008; Grintescu 2009; Jones 2008; Khuenl-Brady 2010; Lemmens 2010).

For two trials (5%), risk of bias assessment was of no relevance, as trial authors presented no TOF-watch data (Rahe-Meyer 2014; Sustic 2012).

The remaining 23 trials (56%) did not provide sufficient data on TOF-watch assessor blinding and had unclear risk of detection bias (Balaka 2011; Carron 2013; Castro 2014; Cheong 2015; Foletto 2014; Gaszynski 2011; Geldner 2012; Georgiou 2013; Hakimoglu 2016; Isik 2016; Kaufhold 2016; Koc 2015; Kogler 2012; Koyuncu 2015; Kvolik 2012a; Kvolik 2012b; Kvolik 2013; Mekawy 2012; Pongracz 2013; Riga 2014; Sabo 2011; Sherman 2014; Tas 2015).

Blinding of safety assessment (detection bias)

Twenty trials (49%) reported adequate blinding of the safety assessor and therefore had low risk of detection bias (Blobner 2010; Brueckmann 2015; Carron 2013; Flockton 2008; Geldner 2012; Jones 2008; Kaufhold 2016; Khuenl-Brady 2010; Lemmens 2010; Martini 2014; Rahe-Meyer 2014; Raziel 2013; Riga 2014; Sabo 2011; Schaller 2010; Sustic 2012; Tas 2015; Woo 2013; Wu 2014; Yagan 2015).

Two trials (5%) did not adequately blind the safety assessor and therefore had high risk of detection bias; one of these specifically reported that the safety assessor was not blinded (Kizilay 2016), and the other trial was marked as an "open-label" study (Grintescu 2009).

The remaining 19 trials (46%) did not provide sufficient data on safety assessor blinding and had unclear risk of detection bias (Adamus 2011; Balaka 2011; Castro 2014; Cheong 2015; Foletto 2014; Gaszynski 2011; Georgiou 2013; Hakimoglu 2016; Illman 2011; Isik 2016; Koc 2015; Kogler 2012; Koyuncu 2015; Kvolik 2012a; Kvolik 2012b; Kvolik 2013; Mekawy 2012; Pongracz 2013; Sherman 2014).

Incomplete outcome data

The following 28 trials (68%) had low risk of attrition bias as either all participants were accounted for, or missing outcome data were properly balanced among groups: Adamus 2011; Blobner 2010; Brueckmann 2015; Carron 2013; Castro 2014; Cheong 2015; Flockton 2008; Gaszynski 2011; Geldner 2012; Hakimoglu 2016; Illman 2011; Isik 2016; Jones 2008; Kaufhold 2016; Kizilay 2016; Koc 2015; Koyuncu 2015; Martini 2014; Mekawy 2012; Pongracz 2013; Rahe-Meyer 2014; Raziel 2013; Riga 2014; Sabo 2011; Tas 2015; Woo 2013; Wu 2014; Yagan 2015.

For three trials (7%), missing outcome data were not balanced across intervention groups (Khuenl-Brady 2010; Lemmens 2010; Schaller 2010); these studies therefore had high risk of attrition bias.

The remaining 10 trials (24%) did not provide sufficient data on incomplete outcomes and had unclear risk of attrition bias (Balaka 2011; Foletto 2014; Georgiou 2013; Grintescu 2009; Kogler 2012; Kvolik 2012a; Kvolik 2012b; Kvolik 2013; Sherman 2014; Sustic 2012).

Selective reporting

Twenty trials (49%) had low risk of reporting bias, as they were registered online: 16 on clinicaltrials.gov (Blobner 2010 – NCT00451217; Brueckmann 2015 – NCT01479764; Flockton 2008 - NTC00451100; Geldner 2012 – NCT00724932; Georgiou 2013 - NCT01629394; Jones 2008 - NCT00473694; Khuenl-Brady 2010 – NCT00451217; Lemmens 2010 – NCT00473694; Martini 2014 – NCT 01631149; Rahe-Meyer 2014 – NCT01422304; Raziel 2013 – NCT01631396; Riga 2014 – NCT02419352; Schaller 2010 – NCT00895609; Woo 2013 – NCT01050543; Wu 2014 – NCT00825812; Yagan 2015 – NCT02215382); one on SYNABA – The Polish Clinical Trials authorization (Gaszynski 2011 – 252922); one on ANZCTR - Australian New Zealand Clinical Trials Registry (Hakimoglu 2016 - ACTRN12614000651684); and finally two on Eudra-CT (Illman 2011 - 2009-013537-22; Pongracz 2013 - 2011-001683-22).

The remaining 20 trials (49%) were not registered online, but it is clear that the published article or meeting abstract includes all expected outcomes (Adamus 2011; Balaka 2011; Carron 2013; Castro 2014; Cheong 2015; Grintescu 2009; Isik 2016; Kaufhold 2016; Kizilay 2016; Koc 2015; Kogler 2012; Koyuncu 2015; Kvolik 2012a; Kvolik 2012b; Kvolik 2013; Mekawy 2012; Sabo 2011; Sherman 2014; Sustic 2012; Tas 2015). Therefore, these trials had low risk of reporting bias.

One trial (2%) did not provide sufficient information for assessment of risk of bias and had unclear risk of reporting bias (Foletto 2014).

Other potential sources of bias

Funding bias

Merck, Sharp and Dohme or Schering-Plough provided financial support for 11 trials (27%), indicating high risk of funding bias (Blobner 2010; Geldner 2012; Illman 2011; Jones 2008; Khuenl-Brady 2010; Lemmens 2010; Martini 2014; Rahe-Meyer 2014; Sabo 2011; Woo 2013; Wu 2014). Authors of the following trials were former employees, current employees, or members of advisory

boards of Merck, Sharp and Dohme/Schering-Plough, or had received honoraria for lectures, consultancy, or advisory board membership, or travel grants from Merck, Sharp and Dohme/Schering-Plough: Adamus 2011; Blobner 2010; Brueckmann 2015; Carron 2013; Flockton 2008; Gaszynski 2011; Geldner 2012; Illman 2011; Kaufhold 2016; Khuenl-Brady 2010; Koyuncu 2015; Lemmens 2010; Martini 2014; Rahe-Meyer 2014 , Schaller 2010; Woo 2013; Wu 2014). These studies had high risk of funding bias.

We could not assess funding risk of bias for the following 14 trials (34%) owing to insufficient information: Balaka 2011; Castro 2014; Foletto 2014; Grintescu 2009; Hakimoglu 2016; Koc 2015; Kogler 2012; Kvolik 2012a; Kvolik 2012b; Kvolik 2013; Mekawy 2012; Pongracz 2013; Sherman 2014; Sustic 2012; these studies had unclear risk of funding bias.

Eight trials (20%) had low risk of funding bias, as they were funded by departmental sources (Georgiou 2013; Isik 2016; Kaufhold 2016; Koyuncu 2015; Raziel 2013; Riga 2014; Schaller 2010; Tas 2015). Trial authors funded two trials (5%) (Kizilay 2016; Yagan 2015), and in two cases (5%), study authors received research grants (Gaszynski 2011; Polish Government grant; and Cheong 2015; Inje University research grant).

Other bias

Twenty-one trials (51%) had low risk of other bias, as they reported specific information on sample size calculation (Adamus 2011; Blobner 2010; Brueckmann 2015; Carron 2013; Cheong 2015; Flockton 2008; Geldner 2012; Hakimoglu 2016; Illman 2011; Isik 2016; Jones 2008; Kaufhold 2016; Koyuncu 2015; Lemmens 2010; Martini 2014; Pongracz 2013; Rahe-Meyer 2014; Sabo 2011; Woo 2013; Wu 2014; Yagan 2015).

Of these 21 trials, 12 (29%) were powered to address this review's primary outcome (Adamus 2011; Blobner 2010; Carron 2013; Cheong 2015; Flockton 2008; Illman 2011; Jones 2008; Lemmens 2010; Pongracz 2013; Sabo 2011; Woo 2013; Wu 2014), and seven trials (17%) were powered to address this review's secondary outcome (Brueckmann 2015; Geldner 2012; Hakimoglu 2016; Isik 2016; Koyuncu 2015; Rahe-Meyer 2014; Yagan 2015). Twenty trials (49%) did not provide information on sample size calculation (Balaka 2011; Castro 2014; Foletto 2014; Gaszynski 2011; Georgiou 2013; Grintescu 2009; Khuenl-Brady 2010; Kizilay 2016; Koc 2015; Kogler 2012; Kvolik 2012a; Kvolik 2012b; Kvolik 2013; Mekawy 2012; Raziel 2013; Riga 2014; Schaller 2010; Sherman 2014; Sustic 2012; Tas 2015).

Treatment groups were generally comparable with respect to baseline characteristics, except Cheong 2015, which described significant differences in body weight between groups that might have influenced the dosage of administered drugs; and Flockton 2008, which reported a higher proportion of women, higher mean age, and a higher percentage of ASA II to III participants in the sugammadex group. Furthemore, Lemmens 2010 discontinued one intervention group owing to a marked difference in efficacy between groups after interim analysis. Therefore, these trials had high risk of other bias.

All trials used the same method (acceleromyography) and at the same monitor site (ulnar nerve, adductor pollicis muscle). We analysed quality variables of neuromuscular recording methods among full-text trials have provided a summary in Table 2 - Quality variables of neuromuscular monitoring methods among included trials.

Effects of interventions

See: **Summary of findings for the main comparison** Sugammadex 2.0 mg/kg vs neostigmine 0.05 mg/kg; **Summary of findings 2** Sugammadex 4.0 mg/kg vs neostigmine 0.07 mg/kg; **Summary of findings 3** Sugammadex (any dose) vs neostigmine (any dose)

See Summary of findings for the main comparison; Summary of findings 2; and Summary of findings 3.

Comparison 1. Sugammadex 2 mg/kg versus neostigmine 0.05 mg/kg for rocuronium reversal

1.1 Primary outcome 1: recovery time from T2 to TOFR > 0.9

Ten trials were included in this category (Blobner 2010; Cheong 2015; Foletto 2014; Gaszynski 2011; Georgiou 2013; Grintescu 2009; Illman 2011; Koc 2015; Woo 2013; Wu 2014).

All trials used rocuronium for intubation and maintenance. The intubating dose of rocuronium was 0.6 mg/kg in five trials (Blobner 2010; Cheong 2015; Koc 2015; Woo 2013; Wu 2014), 0.6 to 1 mg/kg in Illman 2011, and 1 mg/kg in Gaszynski 2011 . The maintenance dose of rocuronium was 0.1 to 0.2 mg/kg in four trials (Blobner 2010; Koc 2015; Woo 2013; Wu 2014), 0.06 mg/kg corrected body weight (CBW) with maximum two additional doses in Gaszynski 2011, and 5 to 10 mg in two trials (Cheong 2015; Illman 2011). No information on rocuronium dosage was available for three trials (Foletto 2014; Georgiou 2013; Grintescu 2009).

Meta-analysis of results showed that sugammadex 2 mg/kg reversed neuromuscular blockade from T2 to TOFR > 0.9 in 1.96 minutes, and neostigmine 0.05 mg/kg reversed neuromuscular blockade from T2 to TOFR > 0.9 in 12.87 minutes. 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 (MD 10.22 minutes, 95% CI 8.48 to 11.96; I^2 = 84%; 10 studies; n = 835; random-effects model; Analysis 1.1; GRADE quality of evidence: moderate; Summary of findings for the main comparison). We downgraded the GRADE quality of evidence by one owing to high risk of bias.

The following trials used NMBAs other than rocuronium and therefore were not included in the meta-analysis.

Flockton 2008 compared rocuronium-sugammadex 2 mg/kg versus cisatracurium-neostigmine 0.05 mg/kg and found that reversal with sugammadex was 4.7 times faster than with neostigmine (geometric mean recovery time of 1.9 vs 9.0; P < 0.0001).

Khuenl-Brady 2010 investigated the effect of sugammadex 2 mg/kg versus neostigmine 0.05 mg/kg in reversing vecuronium-induced neuromuscular blockade (induction 0.1 mg/kg, maintenance 0.03 to 0.03 mg/kg) and described that the geometric mean time of recovery to TOFR > 0.9 was significantly faster with sugammadex than with neostigmine (2.7 minutes, 95% CI 2.2 to 3-3 vs 17.9, 95% CI 13.1 to 24.3, respectively; P < 0.0001; n = 93).

Other trials did not provide enough information or compared doses of sugammadex and neostigmine other than those previously mentioned and as such could not be included in the meta-analysis: Kvolik 2012a compared sugammadex 2 mg/kg versus neostigmine

0.05 mg/kg and reported T2 to TOFR > 0.9 recovery time of 2.5 minutes versus 8.5 minutes, respectively (P = 0.045, n = 38), but these data could not be included in the meta-analysis, as standard deviation (SD) data were not reported in the paper and could not be obtained. Mekawy 2012 examined recovery time from T2 to TOFR > 0.9 comparing sugammadex 4 mg/kg (n = 20) versus neostigmine 0.05 mg/kg plus atropine 0.02 mg/kg (n = 20) and reported that mean reversal time (SD) was 2.47 (0.51) versus 24.21 (4.7) minutes, respectively.

Subgroup analysis

1.2 TIVA versus volatile anaesthetics

Seven trials maintained anaesthesia with volatile anaesthetic (Blobner 2010; Cheong 2015; Gaszynski 2011; Grintescu 2009; Illman 2011; Koc 2015; Woo 2013), and three trials used TIVA for maintenance (Foletto 2014; Georgiou 2013; Wu 2014). Subgroup analysis of results showed no significant subgroup differences in recovery time to TOFR > 0.9 (Analysis 1.2).

Sensitivity analysis

1.3. Excluding meeting abstracts

Sensitivity analysis that excluded data from meeting abstracts (MD 9.27 minutes, 95% CI 7.40 to 11.14; I^2 = 82%; n = 767; random-effects model; Analysis 1.3) did not change overall results regarding significance.

Primary outcome 2: recovery time from PTC 1 to 5 to TOFR > 0.9

This outcome is not clinically relevant as dosages of sugammadex 2 mg/kg and neostigmine 0.05 mg/kg are too low to reverse the deep rocuronium-induced neuromuscular blockade seen at PTC 1 to 5.

Secondary outcomes: risk of adverse events and risk of serious adverse events

We have described these outcomes in detail under Comparison 3 (Analysis 3.2).

Comparison 2. Sugammadex 4 mg/kg versus neostigmine 0.07 mg/kg for rocuronium reversal

Primary outcome 1. Recovery time from T2 to TOFR > 0.9

This outcome is not clinically relevant as dosages of sugammadex 4 mg/kg and neostigmine 0.07 mg/kg are too high to reverse the moderate rocuronium-induced neuromuscular blockade seen at T2.

2.1 Primary outcome 2: recovery time from PTC 1 to 5 to TOFR > 0.9

We combined two trials in this category (Carron 2013; Jones 2008). Both trials used rocuronium 0.6 mg/kg as a single intubating dose and rocuronium 0.15 mg/kg for maintenance. Carron 2013 combined neostigmine with atropine 0.01 mg/kg, and Jones 2008 combined neostigmine with glycopyrrolate 0.014 mg/kg. Carron 2013 administered sugammadex or neostigmine at reappearance of PTC 1 to 5, and Jones 2008 at reappearance of PTC 1 to 2. Carron 2013 included morbidly obese female participants. Carron 2013 maintained anaesthesia with desflurane, and Jones 2008 with sevoflurane.

Meta-analysis of trial results showed that sugammadex 4 mg/kg reversed neuromuscular blockade from PTC 1 to 5 to TOFR > 0.9 in 2.9 minutes, and neostigmine 0.07 mg/kg reversed neuromuscular blockade from PTC 1 to 5 to TOFR > 0.9 in 48.8 minutes. 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 (MD 45.78 minutes, 95% CI 39.41 to 52.15; I^2 = 0%; two studies; n = 114; random-effects model; Analysis 2.1; GRADE quality of evidence: low; Summary of findings 2). We downgraded GRADE quality of evidence two levels owing to high risk of bias and imprecision.

The following trials used NMBAs other than rocuronium, gave a dose of neostigmine different from the one described above, or had missing SD values and were not included in the meta-analysis. Lemmens 2010 investigated the effect of sugammadex 4 mg/kg versus neostigmine 0.07 mg/kg in reversing vecuronium-induced neuromuscular blockade (induction 0.1 mg/kg, maintenance 0.015 mg/kg) and described that the geometric mean time of recovery to TOFR > 0.9 was 15-fold faster with sugammadex than with neostigmine (4.5 vs 66.2 minutes, respectively; P < 0.0001; n = 83). Geldner 2012 reported that participants receiving sugammadex 4 mg/kg administered at PTC 1 to 2 recovered 3.4 times faster than those given neostigmine 0.05 mg/kg plus atropine 0.01 mg/kg (geometric mean recovery time of 2.4 (2.1 to 2.7) vs 8.4 (7.2 to 9.8) minutes, respectively; P < 0.0001). Kogler 2012, reported that median recovery time from PTC 1 to 2 to TOFR > 0.9 after sugammadex 2 mg/kg was 1.1 minutes versus 10.13 minutes for neostigmine 0.07 mg/kg (P < 0.001; n = 31; no SD value reported).

Secondary outcomes: risk of adverse events and risk of serious adverse events

We have described these outcomes in detail under Comparison 3 (Analysis 3.2).

Other recovery times

Some trials measured recovery times other than those described in the comparisons above. Only single trials measured these data; therefore, we could not include them in the meta-analysis, but we can describe the qualitative data as follows.

Balaka 2011 reported mean recovery time from TOFR of 50% to > 90% as 9.7 minutes after administration of neostigmine 2.5 mg and 2.8 minutes after administration of sugammadex 4 mg/kg (P < 0.05; n = 40). Yagan 2015 compared sugammadex 2 mg/kg versus neostigmine 0.05 mg/kg administered at T4/T1 20% and found that extubation time (defined as time to TOFR > 0.9) was seven minutes in the neostigmine group and two minutes in the sugammadex group (P > 0.05; n = 36). Martini 2014 compared moderate NMB (T1 to 2) induced by atracurium/mivacurium reversed by neostigmine 1 to 2 mg plus atropine 0.5 to 1 mg (n = 12) versus deep NMB (PTC 1 to 2) induced by high-dose rocuronium and reversed by sugammadex 4 mg/kg (n = 12). Recovery times to TOFR > 0.9 expressed as mean (SD) were, respectively, 10.9 (4.9) versus 5.1 (2.4) (P < 0.01). Pongracz 2013 investigated adequate doses for reversal of reappearance of four twitches of TOF and discovered that sugammadex 1 mg/kg, unlike neostigmine, rapidly and effectively reverses rocuronium-induced block that has recovered spontaneously to threshold TOF count four. Furthermore, sugammadex 0.5 mg/kg reverses a similar block within eight minutes. Sabo 2011 compared sugammadex 4.0 mg/kg versus neostigmine 0.05 mg/kg plus glycopyrrolate 0.01 mg/kg administered when the TOF-blinded anaesthesiologist considered

the patient ready for reversal of NMB. The anaesthesiologist could ask the TOF-watch operator whether the patient had recovered to at least 1 to 2 PTC before administering the reversal agent. This trial demonstrated significantly faster recovery to TOFR > 0.9 ratio within two minutes (95% CI 1.8 to 2.5) in the sugammadex group versus eight minutes (95% CI 3.8 to 16.5 minutes) in the neostigmine group. Schaller 2010 investigated the efficacy of sugammadex (0.0625, 0.125, 0.25, 0.5, or 1.0 mg/kg), neostigmine (5, 8, 15, 25, or 40 µg/kg), and saline, and by using a bi-exponential model and regression analysis concluded that sugammadex 0.22 mg/kg and neostigmine 34 µg/kg effectively and comparably reverse a rocuronium-induced shallow residual neuromuscular block at TOFR = 0.5 (n = 99). Kaufhold 2016 investigated several different doses of sugammadex or neostigmine as well as placebo administered at TOFR ≥ 0.2 and found that residual neuromuscular block of TOFR = 0.2 cannot be reversed reliably with neostigmine within 10 minutes. However, substantially lower doses of sugammadex than the approved dose of 2.0 mg/kg may be sufficient to reverse residual rocuronium-induced neuromuscular block at recovery of TOFR ≥ 0.2. Koyuncu 2015 looked at the effects of sugammadex 2 mg/kg (n = 50) versus neostigmine 70 µg/kg + atropine 0.4 mg per 1 mg neostigmine administered when four twitches of TOF were visible with fade and found that sugammadex speeds recovery of neuromuscular strength but only slightly (P > 0.01; n = 100).

Comparison 3. Sugammadex (any dose) versus neostigmine (any dose)

Primary outcome 1: recovery time from T2 to TOFR > 0.9

This outcome was not clinically relevant as doses for sugammadex and neostigmine used are specific to the depth of the neuromuscular blockade.

Primary outcome 2: recovery time from PTC 1 to 5 to TOFR > 0.9

This outcome was not clinically relevant as doses for sugammadex and neostigmine used are specific to the depth of the neuromuscular blockade.

3.1. Secondary outcomes: risks of adverse events and serious adverse events

The following 28 trials investigated adverse events possibly, probably, or definitely related to study drug: Adamus 2011; Balaka 2011; Blobner 2010; Brueckmann 2015; Carron 2013; Castro 2014; Cheong 2015; Flockton 2008; Gaszynski 2011; Geldner 2012; Hakimoglu 2016; Illman 2011; Jones 2008; Kaufhold 2016; Khuenl-Brady 2010; Kizilay 2016; Koc 2015; Kogler 2012; Koyuncu 2015; Kvolik 2012a; Lemmens 2010; Mekawy 2012; Pongracz 2013; Sabo 2011; Schaller 2010; Woo 2013; Wu 2014; Yagan 2015 .

Meta-analysis of trial results showed significantly fewer adverse events in the sugammadex group than in the neostigmine group (RR 0.60, 95% CI 0.49 to 0.74; I^2 = 40%; 28 studies, n = 2298; random-effects model; Analysis 3.1; GRADE quality of data: moderate; Summary of findings 3; quality of evidence downgraded one level owing to high risk of bias). Specifically, the risk of composite adverse events was 283/1000 in the neostigmine group and 159/1000 in the sugammadex group. With number needed to treat for an additional beneficial outcome (NNTB) of eight to avoid an adverse event, sugammadex appears to have a stronger safety profile than neostigmine. Furthermore, data show significantly fewer participants with one or more adverse events (RR 0.62, 95% CI 0.48 to 0.81; I^2 = 0%; n = 1766; random-effects model; Analysis 3.5; GRADE quality of data: moderate; Summary of findings 3) in the sugammadex group than in the neostigmine group.

Data on specific adverse events show significantly less risk of the following adverse events in the sugammadex group than in the neostigmine group: bradycardia (RR 0.16, 95% CI 0.07 to 0.34; I^2 = 0%; n = 1218; random-effects model; Analysis 3.6; NNTB 14; GRADE quality of data: moderate; Summary of findings 3; downgraded one level owing to high risk of bias), PONV (RR 0.52, 95% CI 0.28 to 0.97; I^2 = 0%; n = 389; random-effects model; Analysis 3.7; NNTB 16; GRADE quality of data: low; Summary of findings 3; downgraded two levels owing to high risk of bias and imprecision), desaturation (RR 0.23, 95% CI 0.06 to 0.83; I^2 = 0%; n = 134; random-effects model; Analysis 3.8), need for transitory oxygen supplementation (RR 0.24, 95% CI 0.09 to 0.66; I^2 = 0%; n = 76; random-effects model; Analysis 3.10), and procedural complications (RR 0.12, 95% CI 0.02 to 0.97; n = 168; I^2 = 0%; random-effects model; Analysis 3.9). Also, significantly fewer participants were unable to perform 5 seconds of sustained head-lift at extubation (RR 0.34, 95% CI 0.15 to 0.78; I^2 = 0%; n = 395; random-effects model; Analysis 3.11) in the sugammadex group than in the neostigmine group.

Data show no significant differences between sugammadex and neostigmine with regard to nausea (RR 0.83, 95% CI 0.44 to 1.56; I^2 = 0%; n = 719; Analysis 3.13), vomiting (RR 2.05, 95% CI 0.50 to 8.48; I^2 = 0%; n = 297; Analysis 3.14), postprocedural nausea (RR 1.39, 95% CI 0.27 to 7.12; I^2 = 0%; n = 168; Analysis 3.15), headache (RR 1.02, 95% CI 0.48 to 2.18; I^2 = 0%; n = 388; Analysis 3.16), hypertension (RR 1.45, 95% CI 0.23 to 9.05; I^2 = 0%; n = 287; Analysis 3.17), hypotension (RR 1.23, 95% CI 0.38 to 3.96; I^2 = 0%; n = 465; Analysis 3.18), cough (RR 1.42, 95% CI 0.42 to 4.81; I^2 = 65%; n = 200; Analysis 3.19), dry mouth (RR 0.44, 95% CI 0.10 to 1.87; I^2 = 17%; n = 289; Analysis 3.20), dizziness (RR 0.98, 95% CI 0.10 to 9.23; I^2 = 0%; n = 168; Analysis 3.21), tachycardia (RR 0.44, 95% CI 0.09 to 2.22; I^2 = 0%; n = 338; Analysis 3.22), pruritus (RR 1.62, 95% CI 0.20 to 12.88; I^2 = 0%; n = 175; Analysis 3.23), pyrexia (RR 1.43, 95% CI 0.23 to 8.91; I^2 = 0%; n = 264; Analysis 3.24), shivering (RR 0.75, 95% CI 0.40 to 1.43; I^2 = 0%; n = 190; Analysis 3.25), chills (RR 4.04, 95% CI 0.46 to 35.85; I^2 = 0%; n = 166; Analysis 3.26), rash (RR 0.83, 95% CI 0.17 to 3.96; I^2 = 0%; n = 701; Analysis 3.27), supraventricular extrasystoles (RR 0.32, 95% CI 0.03 to 3.05; I^2 = 0%; n = 189; Analysis 3.28), laryngospasm (RR 0.34, 95% CI 0.07 to 1.65; I^2 = 0%; n = 100; Analysis 3.29), increased upper airway secretion (RR 0.37, 95% CI 0.09 to 1.59; I^2 = 0%; n = 442; Analysis 3.30), procedural complications (RR 0.12, 95% CI 0.02 to 0.97; I^2 = 0%; n = 168; Analysis 3.9), procedural hypertension (RR 1.65, 95% CI 0.33 to 8.21; I^2 = 0%; n = 267; Analysis 3.31), procedural hypotension (RR 0.49, 95% CI 0.02 to 14.15; I^2 = 60%; n = 391; Analysis 3.32), abdominal pain (RR 0.98, 95% CI 0.10 to 9.27; I^2 = 0%; n = 196; Analysis 3.33). Furthermore, data show no significant differences in reported clinical signs of residual NMB (RR 1.0; n = 646; Analysis 3.34), inadequate reversal of NMB (RR 0.11, 95% CI 0.01 to 2.02; n = 368; Analysis 3.35), and recurrence of NMB (RR 0.74, 95% CI 0.05 to 10.74; I^2 = 33; n = 1289; Analysis 3.36). Clinical tests revealed no significant differences in the number of participants reporting general muscle weakness at extubation (RR 0.61, 95% CI 0.31 to 1.18; I^2 = 0%; n = 288; Analysis 3.12), at PACU discharge (RR 0.49, 95% CI 0.12 to1.90; I^2 = 0%; n = 410; Analysis 3.37), or in the

number of participants unable to perform five seconds of sustained head-lift at PACU discharge (RR 1.0; n = 399; Analysis 3.38).

A single trial observed some drug-related adverse events; therefore, we could not include them in a meta-analysis of specific adverse events, but we used the data to calculate overall risk of adverse events. The following isolated adverse events were observed in the sugammadex group: three cases of breath-hold (10%) in Hakimoglu 2016 , two cases of strange taste in the mouth (6%) in Gaszynski 2011 , two cases of increased beta-N-acetyl-D-glucosaminidase (6%) in Flockton 2008, two cases of bronchospasm (4%) in Koyuncu 2015, and one case of each of the following: severe abdominal pain (2%), pharyngolaryngeal pain (2%), diarrhoea (2%), and tinnitus (2%) in Blobner 2010 ; decreased hematocrit (1%) and procedural haemorrhage (1%) in Brueckmann 2015; tremor (3%) and altered facial sensation (3%) in Flockton 2008 ; postprocedural hypertension (3%), paraesthesia (3%), and increased blood creatinine phosphokinase (3%) in Jones 2008 ; retching (2%), airway complication to anaesthesia (2%), and hot flush (2%) in Khuenl-Brady 2010; procedural pain (2%) in Sabo 2011; leukocytosis (2%) in Lemmens 2010 ; mild hypoventilation (1%) in Wu 2014; and finally one case of intraoperative movement (2%) in Schaller 2010 .

In the neostigmine group, the following isolated drug-related adverse events were reported: four cases of breath-hold (13%) in Hakimoglu 2016 ; two cases of albumin present in the urine (4%) in Blobner 2010; two cases of leukocytosis (5%) in Lemmens 2010; and one case of each of the following: involuntary muscle contractions (2%), visual accommodation disorder (2%), increased urine beta-2 microglobulin (2%), severe bradycardia (2%), and productive cough (2%) in Blobner 2010 ; respiratory distress (1%) and delayed recovery from anaesthesia (1%) in Brueckmann 2015; hyperhidrosis (3%), decreased blood protein (3%), restlessness (3%), chest discomfort (3%), incision site complication (3%), and postprocedural complication (3%) in Jones 2008 ; ventricular extrasystoles (2%), sleep disorder (2%), and increased gamma-glutamyltransferase (2%) in Khuenl-Brady 2010 ; anxiety (3%), depression (3%), and fatigue (3%) in Lemmens 2010 ; dyspepsia (2%) and somnolence (2%) in Sabo 2011; severe muscle weakness (1%) in Wu 2014; and finally one case of intraoperative movement (2%) in Schaller 2010.

We have described in Table 3 each observed adverse event possibly, probably, or definitely related to sugammadex or neostigmine. This table also presents risk of adverse events in descending order, as well as the number of studies observing each adverse event.

The largest trial in this review (Rahe-Meyer 2014) randomized 1198 participants and reported that 64 out of 596 participants (10.7%) in the sugammadex group and 72 out of 588 (12.2 %) in the usual care group had at least one drug-related adverse event. Unfortunately, we could not include these data in our meta-analysis, as the "usual care" group combined participants who received either neostigmine or placebo, and we were not able to obtain data from the neostigmine group.

Subgroup analysis of composite adverse events

3.2 Different dosages of sugammadex and neostigmine

Different trials used different dosages of sugammadex and neostigmine.

Adamus 2011 compared sugammadex 2 mg/kg versus neostigmine 0.04 mg/kg. Twelve trials compared sugammadex 2 mg/kg versus neostigmine 0.05 mg/kg (Blobner 2010; Castro 2014; Cheong 2015; Flockton 2008; Gaszynski 2011; Illman 2011; Khuenl-Brady 2010; Koc 2015; Kvolik 2012b; Woo 2013; Wu 2014; Yagan 2015). Two trials compared sugammadex 2 mg/kg versus neostigmine 0.07 mg/kg (Kogler 2012; Koyuncu 2015). Balaka 2011 compared sugammadex 2 mg/kg versus neostigmine 2.5 mg. Kizilay 2016 compared sugammadex 3 mg/kg versus neostigmine 0.03 mg/kg. Four trials compared sugammadex 4 mg/kg versus neostigmine 0.05 mg/kg (Geldner 2012; Hakimoglu 2016; Mekawy 2012; Sabo 2011). Three trials compared sugammadex 4 mg/kg versus neostigmine 0.07 mg/kg (Carron 2013; Jones 2008; Lemmens 2010). Four trials compared several different doses of sugammadex versus several different doses of neostigmine (Brueckmann 2015; Kaufhold 2016; Pongracz 2013; Schaller 2010). Subgroup analysis of data showed no significant subgroup differences in RR for composite adverse events (Analysis 3.2).

3.3. TIVA versus volatile anaesthetics

Twenty trials maintained anaesthesia with volatile anaesthetic (Adamus 2011; Blobner 2010; Brueckmann 2015; Carron 2013; Castro 2014; Cheong 2015; Gaszynski 2011; Hakimoglu 2016; Illman 2011; Jones 2008; Khuenl-Brady 2010; Kizilay 2016; Koc 2015; Koyuncu 2015; Lemmens 2010; Mekawy 2012; Pongracz 2013; Sabo 2011; Woo 2013; Yagan 2015). Seven trials used TIVA for maintenance (Flockton 2008; Geldner 2012; Kaufhold 2016; Kogler 2012; Kvolik 2012b; Schaller 2010; Wu 2014). One trial provided insufficient information (Balaka 2011). Subgroup analysis of trial results showed no significant subgroup differences in RR for composite adverse events (Analysis 3.3).

Sensitivity analysis of composite adverse events

3.4 Excluding meeting abstracts

Sensitivity analysis excluding data from meeting abstracts (RR 0.60, 95% CI 0.49 to 0.74; I^2 = 35%; n = 2091; random-effects model; Analysis 3.4) did not change overall results regarding significance.

Subgroup analysis of bradycardia

3.7 Atropine versus glycopyrrolate

All trials reporting bradycardia combined neostigmine with an antimuscarinic drug. Six trials used atropine (Carron 2013; Gaszynski 2011; Geldner 2012; Koc 2015; Koyuncu 2015; Wu 2014). Five trials used glycopyrrolate (Blobner 2010; Brueckmann 2015; Cheong 2015; Schaller 2010; Woo 2013). Subgroup analysis of trial results showed no significant subgroup differences in RR for bradycardia (Analysis 3.6).

Subgroup analysis of PONV

3.9 TIVA versus volatile anaesthetics

Five trials maintained anaesthesia with volatile anaesthetic (Adamus 2011; Castro 2014; Cheong 2015; Hakimoglu 2016; Yagan 2015), One trial used TIVA for maintenance (Schaller 2010). Subgroup analysis of trial results showed no significant subgroup differences in RR for PONV (Analysis 3.7).

Qualitative data

Investigators reported effects of sugammadex and neostigmine on the following parameters in data format that was ineligible for meta-analysis.

Intraocular pressure (IOP)

Hakimoglu 2016 described that post-extubation intraocular pressures (IOPs) were similar between sugammadex and neostigmine groups (P > 0.05; n = 60); Yagan 2015 reported lower end-extubation IOPs when sugammadex 2 mg/kg was used in comparison with neostigmine 0.05 mg/kg - atropine 0.02 mg/kg (P < 0.05; n = 36), suggesting that sugammadex may be a better option for reversal of neuromuscular blockade in conditions for which an increase in IOP is not desired, such as glaucoma and penetrating eye injury.

Haemodynamic effects

Kizilay 2016 (n = 90) examined the haemodynamic effects of sugammadex and neostigmine in cardiac participants undergoing non-cardiac surgery. Investigators found that the sugammadex group had lower systolic, diastolic, and mean blood pressures and heart rate when compared with the neostigmine group (P < 0.05). They reported no significant differences between and within groups in terms of QTc interval values. Study authors suggest that sugammadex might be preferred to neostigmine-atropine combination for reversal of rocuronium-induced neuromuscular blockade in cardiac patients undergoing non-cardiac surgery,

Bleeding events

The largest trial in this review(Rahe-Meyer 2014; n = 1198) included participants undergoing hip/knee surgery or hip fracture surgery and compared sugammadex 4 mg/kg versus usual care (neostigmine or spontaneous recovery). Investigators reported bleeding events within 24 hours in 17 (2.9%) sugammadex and 24 (4.1%) usual care participants (RR 0.70, 95% CI 0.38 to 1.29). Compared with usual care, increases of 5.5% in activated partial thromboplastin time (aPTT; P < 0.001) and 3.0% in prothrombin time (P < 0.001) from baseline occurred with sugammadex 10 minutes after administration and resolved within 60 minutes. Data show no significant differences between sugammadex and usual care for other blood loss measures (transfusion, 24-hour drain volume, drop in haemoglobin, and anaemia) or for risk of venous thromboembolism, and trials reported no cases of anaphylaxis. Sugammadex induced limited (< 8% at 10 minutes) and transient (< 1 hour) increases in aPTT and prothrombin time but was not associated with increased risk of bleeding or increased severity of bleeding. A much smaller trial (Tas 2015; n = 50) investigated effects of sugammadex and neostigmine on postoperative coagulation parameters and bleeding after seroplasty with sugammadex, increasing postoperative bleeding measured by nasal tip dressings (4.1 ± 2.7 mL in the sugammadex group vs 2.5 ± 2.7 mL in the neostigmine group; P = 0.013) without significantly affecting prothrombin time (PT) (P = 0.953), aPTT values (P = 0.734), or international normalized ratio (INR) values (P = 0.612).

Mekawy 2012 reported no differences in intraoperative blood loss between sugammadex 4 mg/kg (n = 20) and neostigmine 0.05 mg/kg plus atropine 0.02 mg/kg groups (104.6 ± 13.2 vs 111.2 ± 9.8 mL, respectively; P = 0.060)

Renal function

Isik 2016 (n = 50) investigated effects of neostigmine and sugammadex on kidney function and found that both drugs may affect kidney function but sugammadex has more tolerable effects than neostigmine.

Gastric emptying

Sustic 2012 measured gastric emptying by using the paracetamol absorption test. Values of plasma paracetamol concentration (PPC) immediately after arrival of participants in the recovery room (T0) were significantly higher between the sugammadex 2 mg/kg group (1.2 ± 0.9) and the neostigmine 0.04 mg/kg/atropine 0.015 mg/kg group (0.4 ± 0.4) (P < 0.01). Values of PPC at 15, 30, 60, 120, and 150 minutes were higher without reaching statistical difference: T15, 2.1 ± 1.5 vs 1.5 ± 1.4; T30, 3.7 ± 3.8 vs 2.9 ± 2.2; T60, 4.2 ± 2.8 vs 3.5 ± 2.7; T120, 5.0 ± 3.4 vs 4.6 ± 3.6; and T150, 5.9 ± 3.4 vs 4.9 ± 3.2.

Values for PPC at 90 minutes were minimally higher in the neostigmine-atropine group: time 90, 4.6 ± 3.4 vs 4.7 ± 3.4 (P = NS). Study authors concluded that although results show a tendency toward faster gastric emptying in the sugammadex group, this difference did not reach statistical difference, possibly owing to the small sample size of the study .

Thyroid function

Kvolik 2012a (n = 24) investigated effects on thyroid function and observed a significant increase in T4 levels compared with baseline one hour after anaesthesia (from 13.3 to 17.5 in the neostigmine group, and from 12.6 to 16.2 pmol/L in the sugammadex group; P < 0.05) that returned to baseline after 24 hours in both groups. T3 decreased in both groups postoperatively (from 5.2 to 3.5 in the neostigmine group, and from 4.9 to 3.3 pmol/L in the sugammadex group), with no intergroup differences noted (P > 0.05). Mean thyroid-stimulating hormone (TSH) after 24 hours was not different between groups (1.32 in the neostigmine group vs 1.27 pmol/L in the sugammadex group; P = 0.49). In conclusion, sugammadex treatment did not change the levels of thyroid hormones and may be used safely in patients undergoing total thyroidectomy.

Cognitive function

Riga 2014 (n = 114) investigated cognitive function in patients receiving sugammadex or neostigmine and found no significant differences between groups when measuring cognitive function with the mini-mental state evaluation test (P = 0.25), as described in Tombaugh 1992, and the Clock Drawing test (P = 0.06), as described in Agrell 1998.

Postoperative vomiting and nausea (PONV)

Carron 2013 reported higher PONV scores in the neostigmine group than in the sugammadex group (3.2 ± 1.5 vs 1.9 ± 1.3; P = 0.015; n = 40) with no significant difference in antiemetic supplement (7 (35%) vs 3 (15%); P = 0.10).

Tas 2015 compared sugammadex 2 mg/kg (n = 24) versus neostigmine 0.05 mg/kg plus atropine 0.02 mg/kg (n = 26) and reported no differences regarding nausea/vomiting between groups (P = 0.512).

Raziel 2013 (n = 40) observed no differences between sugammadex 2 mg/kg and neostigmine 0.05 mg/kg in nausea/vomiting among morbidly obese participants undergoing bariatric surgery.

Pain

Martini 2014 compared moderate NMB (T1 to T2) induced by atracurium/mivacurium reversed by neostigmine 1 to 2 mg plus atropine 0.5 to 1 mg (n = 12) versus deep NMB (PTC 1 to 2) induced by high-dose rocuronium and reversed by sugammadex 4 mg/kg (n = 12) and found no significant differences in pain score as measured by a 10-point scale (2.6 ± 1.6 vs 2.1 ± 2.2, respectively).

Tas 2015 compared sugammadex 2 mg/kg (n = 24) versus neostigmine 0.05 mg/kg plus atropine 0.02 mg/kg (n = 26) and reported no differences regarding postoperative pain between groups (P = 0.280).

Overall signs of postoperative residual paralysis

We chose the following parameters as overall signs of postoperative residual paralysis: inability to perform 5 second head-lift test and general muscle weakness after extubation and at PACU discharge, amblyopia, asthenia, desaturation < 90%, transitory oxygen supplementation, respiratory distress, respiratory depression, postoperative respiratory complications (evaluated by PRSES – postoperative system evaluation score), moderate dyspnoea, pneumonia, acute lung failure, or symptoms of residual NMB or recurrence of NMB if specifically reported by study authors. The following 15 studies reported any of these adverse events: Balaka 2011; Blobner 2010; Brueckmann 2015; Carron 2013; Flockton 2008; Geldner 2012; Jones 2008; Khuenl-Brady 2010; Koyuncu 2015; Kvolik 2012b; Lemmens 2010; Mekawy 2012; Schaller 2010; Woo 2013; Wu 2014).

Meta-analysis of trial results showed significantly reduced risk of overall signs of postoperative residual paralysis (RR 0.40, 95% CI 0.28 to 0.57; I^2 = 0%; n = 1474; random-effects model; NNTB 13; Analysis 3.39; GRADE quality of evidence: moderate; Summary of findings 3) in the sugammadex group when compared with the neostigmine group. We downgraded GRADE quality of evidence one level owing to high risk of bias.

Investigators reported the following data on overall events of postoperative residual paralysis, which were ineligible for meta-analysis.
Carron 2013 (n = 40) found higher peripheral oxygen saturation levels (SpO_2) levels at recovery admission in the sugammadex group (97 ± 2.3% vs 94.4 ± 4%; P = 0.018), along with faster ability to swallow after extubation (7.1 ± 1.8 minutes vs 12.2 ± 6 minutes; P = 0.0027), and faster ability to get into bed independently (24 ± 9 minutes vs 33.4 ± 12 minutes; P = 0.022) when compared with the neostigmine group.

Foletto 2014 (n = 34) reported that respiratory function was restored more quickly in morbidly obese (MOB) participants who received sugammadex when measured by postoperative forced vital capacity (1.6 ± 0.7 vs 2.41 ± 0.8 L; P < 0.05), forced expiratory volume in one second (1.37 ± 0.7 vs 2.05 ± 0.6 L/s; P < 0.05), and peak expiratory flow 30 minutes postoperatively (2.55 ± 1.7 vs 3.75 ± 1.4 L/s; P < 0.05), but observed no significant differences in spirometry performed 15 minutes postoperatively.

Raziel 2013 (n = 40) observed no differences between sugammadex 2 mg/kg and neostigmine 0.05 mg/kg in respiratory function among morbidly obese participants undergoing bariatric surgery.

Martini 2014 compared moderate NMB (T1 to T2) induced by atracurium/mivacurium reversed by neostigmine 1 to 2 mg plus atropine 0.5 to 1 mg (n = 12) with deep NMB (PTC 1 to 2) induced by high-dose rocuronium and reversed by sugammadex 4 mg/kg (n = 12), and found no significant difference in saturation in PACU (98.6 ± 1.8 vs 98.2 ± 1.4, respectively) or breathing rate in PACU (14.5 ± 2.2 vs 14.5 ± 2.2, respectively).

Sherman 2014 found lower saturation levels (95.8 ± 0.014 vs 96.72 ± 0.01; P < 0.02), lower minimal saturation (93% vs 94%), and no difference in respiratory complications when comparing neostigmine 2.5 mg (n = 25) versus sugammadex 2 mg/kg (n = 32).

Tas 2015 compared sugammadex 2 mg/kg (n = 24) versus neostigmine 0.05 mg/kg plus atropine 0.02 mg/kg (n = 26) and reported no differences between groups regarding saturation levels after extubation (97.6 ± 0.2 vs 98.0 ± 0.2, respectively; P = 0.280).

Furthermore, several trials conducted postoperative neuromuscular monitoring to quantify the risk of residual neuromuscular blockade, defined as TOFR < 0.9: Brueckmann 2015 found that zero out of 74 (0%) sugammadex participants and 33 out of 76 (43.4%) neostigmine participants had TOFR > 0.9 at PACU admission (odds ratio (OR) 0.0, 95% CI 0.0 to 0.6; P < 0.0001). Of the 33 neostigmine participants, 2 also had clinical evidence of residual NMB.

Sabo 2011 described that 2 out of 50 participants (4%) in the sugammadex group had residual NMB (TOFR < 0.9) at the time of extubation compared with 26 out of 43 participants (60.5) in the neostigmine group, although data provided no clinical evidence (i.e. respiratory problems) of residual NMB in either group.

Gaszynski 2011 described that TOF at PACU was 109.8% versus 85.5% (P < 0.05; n = 70) in the sugammadex and neostigmine groups, respectively, and reached > 90% in every case in the sugammadex group but not in the neostigmine group.

No participants experienced recurrence of neuromuscular blockade based on neuromuscular monitoring in Geldner 2012 (n = 133).

Sugammadex (any dose) versus neostigmine (any dose), drug-related serious adverse events (SAEs)

Fourteen trials reported serious adverse events (SAEs) possibly, probably, or definitely related to study drug (Adamus 2011; Blobner 2010; Brueckmann 2015; Flockton 2008; Geldner 2012; Hakimoglu 2016; Jones 2008; Kaufhold 2016; Khuenl-Brady 2010; Koyuncu 2015; Lemmens 2010; Schaller 2010; Woo 2013; Wu 2014). Meta-analysis of trial results showed no significant differences between sugammadex and neostigmine regarding participants with one or more serious adverse events or for composite adverse events (RR 0.54, 95% CI 0.13 to 2.25; I^2 = 0%; ten studies; n = 959; random-effects model; Analysis 3.40; GRADE quality of evidence: low; Summary of findings 3). We downgraded GRADE quality of evidence two levels owing to high risk of bias and imprecision.

Clearly reported drug-related serious adverse events included one case of acute myocardial infarction, pneumonia, and inadequate NMB reversal in the neostigmine group (Brueckmann 2015), one case of acute lung failure in the neostigmine group (Schaller 2010), one case of postoperative upper abdominal pain in the neostigmine group (Geldner 2012), one case of postprocedural haemorrhage in

the sugammadex group (Brueckmann 2015), and finally one case of respiratory depression in the sugammadex group (Koyuncu 2015).

Trial sequential analysis (TSA)

We applied TSA to several outcome data as described in Summary of findings for the main comparison, Summary of findings 2, and Summary of findings 3.

TSA of all trials comparing neostigmine 0.05 mg/kg versus sugammadex 2.0 mg/kg with regard to recovery time from T2 to TOFR > 0.9 minutes indicates that with a required information size of 106, firm evidence sugammadex in a random-effects model, with an alfa-boundary adjusted MD of -10.22 (95% CI -12.11 to -8.33; diversity (D^2) = 87%; I^2 = 84%; random-effects model; Figure 1). The cumulative Z-curve crossed the monitoring boundary constructed for the required information size with 80% power and alpha of 0.05. However, none of the included trials had low risk of bias, and given that TSA is ideally designed for trials with low risk of bias and cannot be adjusted for risk of bias, the precision of our findings has to be downgraded. Furthermore, we found a high degree of diversity and heterogeneity, which once again raises questions about the reliability of the calculated required information size.

TSA of dichotomous data on drug-related risk of adverse events when neostigmine (any dose) was compared with sugammadex (any dose) with continuity adjustment for zero event trials (0.001 in each arm) resulted in an alfa-boundary adjusted RR of 0.62 (95% CI 0.51 to 0.74; diversity (D^2) = 34%; I^2 = 14%; random-effects model; Figure 3), with a control event proportion of 27.97%. With the required information size of 502, analyses provided firm evidence in favour of sugammadex, with 2298 participants included, corresponding to a relative risk reduction (RRR) of 38% with 80% power and alpha of 0.05. Despite the fact that the cumulative Z-curve does not cross the monitoring boundary directly, it is hard to imagine future trials radically changing the overall picture of this analysis. Once again, none of the included trials had low risk of bias and this does downgrade the reliability of our finding.

TSA of dichotomous data on risk of serious adverse events when neostigmine (any dose) was compared with sugammadex (any dose) with continuity adjustment for zero event trials (0.001 in each arm) resulted in an alfa-boundary adjusted RR of 0.35 (95% CI 0.00 to 3190; diversity (D^2) = 0%; I^2 = 0%; random-effects model), with a control event proportion of 1.04%. The cumulative Z-curve does not cross the monitoring boundary constructed for a required information size of 8189 participants, with 11.71% of the required information size included across included trials so far with 80% power and alpha of 0.05. Once again, none of the included trials had low risk of bias and this affects the reliability and precision of our estimates.

TSA of dichotomous data on risk of signs of residual neuromuscular blockade when neostigmine (any dose) was compared with sugammadex (any dose) with continuity adjustment for zero event trials (0.001 in each arm) resulted in an alfa-boundary adjusted RR of 0.4 (95% CI 0.27 to 0.59; diversity (D^2) = 0%; I^2 = 0%; random-effects model), with 80% power and alpha of 0.05 (Figure 4), with a control event proportion of 13.08%. The cumulative Z-curve crosses the monitoring boundary constructed for a required information size of 424 participants, indicating firm evidence in favour of sugammadex. However, as previously described, none of the included trials had low risk of bias and this equally diminishes the reliability and precision of our estimates.

Finally, owing to overall high risks of bias, imprecision, and indirectness involved in assessment of GRADE for the above analysis, one could easily argue that the required power should be 90% - not 80% - by which the required information size would be increased; nevertheless we cannot rule out the direction of results in favour of sugammadex, despite the absence of large trials with low risk of bias.

DISCUSSION

Summary of main results

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 favouring sugammadex. For meta-analyses of primary outcomes, 12 studies (n = 949) were eligible.

Meta-analysis of trial results showed that sugammadex 2 mg/kg reversed NMB from second twitch (T2) to train-of-four ratio (TOFR) > 0.9 in 1.96 minutes, and neostigmine 0.05 mg/kg reversed NMB from T2 to TOFR > 0.9 in 12.87 minutes. Sugammadex 2 mg/kg was therefore on average 10.22 minutes (6.6 times) faster than neostigmine 0.05 mg/kg in reversing NMB at T2 reappearance (mean difference (MD) 10.22 minutes, 95% confidence interval (CI) 8.48 to 11.96; I^2 = 84%; ten studies; n = 835; random-effects model; GRADE quality of evidence: moderate; Analysis 1.1). Reversal time from post-tetanic count (PTC) 1 to 5 to TOFR > 0.9 was not investigated; this was considered clinically irrelevant owing to the doses of sugammadex and neostigmine used for this comparison.

Sugammadex 4 mg/kg reversed NMB from PTC 1 to 5 to TOFR > 0.9 in 2.9 minutes, and neostigmine 0.07 mg/kg reversed NMB from PTC 1 to 5 to TOFR > 0.9 in 48.8 minutes. Sugammadex 4 mg/kg was therefore on average 45.78 minutes (16.8 times) faster than neostigmine 0.07 mg/kg in reversing NMB at PTC 1 to 5 reappearance (MD 45.78 minutes, 95% CI 39.41 to 52.15; I^2 = 0%; n = 114; random-effects model; GRADE quality of evidence: low; Analysis 2.1). Reversal time from T2 to TOFR > 0.9 was not investigated since it was deemed clinically irrelevant owing to the doses of sugammadex and neostigmine used for this comparison.

We found 28 trials (n = 2298) eligible for meta-analysis of the secondary outcomes (risks of adverse events and serious adverse events). We found significantly fewer composite adverse events in the sugammadex group than in the neostigmine group (risk ratio (RR) 0.60, 95% CI 0.49 to 0.74; I^2 = 40%; 28 studies; n = 2298; random-effects model; GRADE quality of data: moderate; Analysis 3.1). 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. Furthermore, significantly fewer participants had one or more adverse events (RR 0.62, 95% CI 0.48 to 0.81; I^2 = 0%; n = 1766; random-effects model; GRADE quality of data: moderate; Analysis 3.5) in the sugammadex group than in the neostigmine group. Review of specific adverse events in the sugammadex group compared

with the neostigmine group revealed significantly less risk of the following adverse events: bradycardia (Analysis 3.6), postoperative nausea and vomiting (PONV) (Analysis 3.7), desaturation (Analysis 3.8), and need for transitory oxygen supplementation (Analysis 3.10). Also, a significantly lower number of participants in the sugammadex group were not able to perform 5 second sustained head-lift at extubation (Analysis 3.11). Data showed no significant differences between sugammadex and neostigmine regarding participants with one or more serious adverse events, nor in composite adverse events (RR 0.54, 95% CI 0.13 to 2.25; I^2 = 0%; ten studies; n = 959; random-effects model; GRADE quality of evidence: low; Analysis 3.40). Reversal time from T2 and PTC 1 to 5 to TOFR > 0.9 was not investigated, as it is clinically irrelevant owing to the doses of sugammadex and neostigmine used for this comparison.

Overall completeness and applicability of evidence

For our primary outcome, we performed a comparison of the effects of sugammadex and neostigmine at two depths of NMB: moderate block as indicated by reappearance of T2, and deep block as indicated by reappearance of PTC 1 to 5 on neuromuscular monitoring. However, administration of neostigmine is not recommended for reversal of deep block and absence of any signs of neuromuscular recovery due to the ceiling effect (Caldwell 2009; Plaud 2010), which is seen when maximal acetylcholine concentration is not sufficient to adequately compete with the muscle relaxant. According to the current prescribing information, this is an off-label indication (www.fda.gov). Nevertheless, our search identified two trials (Carron 2013, Jones 2008) in which sugammadex and neostigmine were used to reverse rocuronium-induced deep NMB, and one trial (Lemmens 2010) in which sugammadex and neostigmine were used to reverse vecuronium-induced deep block. As this was not an exclusion criterion in the original protocol and the data were available, we chose to include these three studies in our review. However, for reasons explained above, the clinical importance of these comparatory findings aside from the obvious faster reversal due to sugammadex remains questionable.

In this context, one could argue that a comparison between sugammadex and neostigmine for reversing a shallow NMB would be more relevant. However, this was not a predefined outcome in the original protocol. Furthermore, our search identified five trials in which some degree of shallow block was indicated (Kaufhold 2016; Koyuncu 2015; Pongracz 2013; Schaller 2010; Yagan 2015), but none of these trials obtained comparable data on recovery time to TOFR > 0.9.

The overall quantity of data on which our conclusions can be based is large, and data were drawn from 41 randomized controlled trials with 4206 participants. According to GRADE, the quality of evidence for most of our meta-analyses is moderate. Most trial participants were adults classified as American Society of Anesthesiologists (ASA) I to III who were undergoing elective surgery, and reported outcomes were relevant in a clinical setting. Primary and secondary outcomes, recovery time to TOFR > 0.9, and adverse effects, were generally well reported. Therefore, on basis of the large number of identified studies and participants, available evidence seems to be applicable to adult patients of ASA classification I to III who are undergoing elective surgery.

According to our meta-analyses, sugammadex 2 mg/kg given at T2 reverses the NMB within 1.96 minutes and 6.6 times (10.22 minutes) faster than neostigmine 0.05 mg/kg (12.87 minutes). Furthermore, sugammadex 4 mg/kg, given to deep NMB at PTC 1 to 5 reappearance, reverses the block in 2.9 minutes and 16.8 times (45.78 minutes) faster than neostigmine 0.07 mg/kg (48.8 minutes).

The time difference offers several potential advantages in that a patient who is paralysed with a neuromuscular blocking agent has to be out of the NMB with TOFR > 0.9 before undergoing tracheal extubation, to avoid adverse effects due to residual paralysis (Eikermann 2006; Murphy 2008; Murphy 2013).

Sugammadex rapidly reverses NMB. This appears favourable because it reduces required anaesthesia time for the patient. Additionally, unlike neostigmine, sugammadex can be administered at any stage during a surgical procedure and independent of the depth of blockade. A reduced duration of anaesthesia not only may improve recovery time for the patient but could potentially reduce costs by saving the time needed for a prolonged awakening and potentially enabling smoother flow of patients through the operating theatre.

The cost-effectiveness of sugammadex was not a predefined outcome of this review. To demonstrate cost-effectiveness of sugammadex, two issues must be established: reduced patient recovery time perioperatively, and translation of any such reduction into resource utilization in terms of freeing up staff to work on productive alternative activities such as caring for other patients. This outcome is very difficult to assess owing to various confounders, such as the organizational structure of each hospital (Dexter 1995), procedural flow, variability of NMB, monitoring and extubation practices, turnover times between procedures, frequency of emergency procedures, operating room overtime resource use, staff payments, productive alternative use of freed resources (Fuchs-Buder 2012; Paton 2010), and finally the cost of available drugs in each country. Furthermore, it is difficult to calculate whether any reduction in adverse events associated with sugammadex, besides improved quality of care, can readily be translated into cost-effectiveness.

One systematic review (Paton 2010) compared the cost-effectiveness of sugammadex versus neostigmine/glycopyrrolate for routine reversal of moderate or profound muscle relaxation produced by rocuronium and vecuronium. Results from included trials (Flockton 2008, Blobner 2010, Lemmens 2010, Jones 2008) indicate that sugammadex 2 mg/kg (4 mg/kg) produces more rapid recovery from moderate NMB than is achieved with neostigmine/glycopyrrolate. Economic assessment indicated that if the reductions in recovery time associated with sugammadex in these trials were replicated in routine clinical practice, sugammadex would be cost-effective if those reductions were achieved in the operating theatre, but not if they were achieved in the recovery room. Review authors went on to conclude that further research is required to evaluate the effects of sugammadex on patient safety, predictability of recovery from NMB, patient outcomes, and efficient use of resources. A recent Canadian study (Insinga 2016) used a discrete model-event simulation to investigate the potential impact of substituting sugammadex for neostigmine on operating room efficiency and incidence of residual NMB. Study authors concluded that the principal impact for patients managed by moderate NMB is likely to be seen as a reduction in the risk of residual NMB and associated complications. For patients maintained at a deep level of block until the procedure is completed, sugammadex was likely to both enhance operating

room efficiency and reduce residual block complications. Last but not least, the cost per anaesthetic case might increase in case of unrestricted use of sugammadex, as shown in a retrospective observational audit (Ledowski 2012).

In conclusion, considerable uncertainties remain regarding the cost-effectiveness of sugammadex, and further investigation is needed. Currently, the cost of sugammadex is relatively high as the result of proprietary rights. The price for the smallest vial (100 mg/mL, 2 mL) in Denmark is around 117 euros. In addition, drug patents are set to expire on 27 January 2021 (Drugs.com). How this will affect the price and clinical usage of sugammadex remains to be established.

Another important clinical consideration in the choice of reversing agent is the risk of adverse effects.

The decision to use a drug is based on an overall assessment of its benefits and harms. Monitoring and reporting of adverse events during a clinical trial constitutes a cumbersome and complex task involving many assumptions and choices, such as adequate blinding of study participants and investigators, distinction between adverse and serious adverse events, causality of adverse events to study drugs, reporting by patients, and finally consistent and transparent monitoring, coding, and reporting by investigators.

Trials included in this review defined, monitored, and reported adverse events in many different ways. Some trials (Blobner 2010; Jones 2008; Lemmens 2010) coded all adverse events and serious adverse events described by the investigator in a systematic way using the Medical Dictionary for Regulatory Activities (MeDRA). Other trials reported symptoms related to study drug administration without necessarily defining them as adverse events (Adamus 2011; Mekawy 2012) - an issue most often seen in meeting abstracts (Balaka 2011; Georgiou 2013; Kvolik 2012b) that is probably due to word count restriction. Furthermore, some included trials specifically addressed causality between adverse events and study drugs by presenting not only adverse events observed regardless of relation to study drug but also adverse events possibly, probably, or definitely related to study drug (Blobner 2010; Jones 2008; Lemmens 2010; Woo 2013), although others did not specifically address this issue (Adamus 2011; Castro 2014; Yagan 2015). Smaller trials with few observed adverse events usually presented all observed adverse events (Balaka 2011; Koc 2015; Koyuncu 2015; Yagan 2015), while bigger trials presented the most frequently occurring adverse events (Brueckmann 2015; Jones 2008; Lemmens 2010; Woo 2013). Additionally, some trials used blinded safety outcome assessors (Blobner 2010; Brueckmann 2015; Carron 2013; Flockton 2008; Woo 2013) in contrast to others (Grintescu 2009; Kizilay 2016). Last but not least, very few of the included trials were designed and powered to address safety as a primary outcome (Brueckmann 2015; Rahe-Meyer 2014).

As explained earlier in the Methods and Results sections, overall clinical signs of postoperative residual paralysis such as inability to perform 5 second head-lift and general muscle weakness observed in some trials (Blobner 2010; Flockton 2008; Jones 2008; Khuenl-Brady 2010; Lemmens 2010) were regarded as adverse events in this review. Furthermore, we decided to include reported symptoms related to drug administration as adverse events, even though they were not specifically defined as adverse events, to avoid potentially dismissing good quality data because of lack of correct phrasing. We have addressed and explained under the notes section in Characteristics of included studies any discrepancy in adverse events presented in the original article and in this review due to definitions of adverse events or additional data about adverse events supplied through email correspondence with trial authors. Readers of medical journals and of this review need to be aware of these issues as they appraise this review and the literature critically.

Included trials provided sparse data regarding which body weight dose calculations were based upon (i.e. ideal, correlated, or lean body weight), and we were unable to retrieve additional data that would shed light on this. As a consequence, we have regarded the weight data provided as total body weight.

Our results show an overall significantly lower risk of adverse events in the sugammadex group than in the neostigmine group (Analysis 3.1; Analysis 3.5), along with an NNTB of eight for avoidance of an adverse event.

Data show significantly less risk of the clinically important adverse effect PONV (Analysis 3.7) and less risk of overall signs of postoperative residual paralysis in the sugammadex group (Analysis 3.39), making this treatment preferable because residual blockade increases the risk of serious adverse effects such as acute respiratory failure (Murphy 2008; Sauer 2011). Data also show reduced risk of bradycardia (Analysis 3.6) in the sugammadex group. However, the two groups reported many adverse reactions similarly, as presented in the Results section. Results show that no cases of anaphylaxis were reported.

Our results may not be directly applicable to all groups of patients because sugammadex may have different outcomes for patients with higher ASA classes and for patients with special comorbidities or systemic dysfunction.

These patients are not represented well in the trials included in our meta-analyses, but lower risk of adverse effects as well as sufficient reversal from neuromuscular blockade may be even more beneficial for this group of patients, and inclusion of these more fragile patients in future trials could potentially reduce the NNTB for avoidance of adverse events. However, this might not be applicable to all patient groups (e.g.. severe renal impairment has been discussed as a possible contraindication to treatment. Sugammadex is excreted unchanged in the urine by the kidneys. Renal clearance of sugammadex is rapid, with most of the dose (70%) excreted within six hours (Golembiewski 2016). None of the included trials enrolled participants with renal dysfunction. However, Isik 2016 (n = 50) investigated the effects of neostigmine and sugammadex on adults of ASA I to II with normal renal function and found that both drugs may impair renal function, but sugammadex was more tolerable than neostigmine. A pharmacokinetic study (Staals 2010) investigated the pharmacokinetics of sugammadex 2 mg/kg and of rocuronium 0,6 mg/kg in 15 participants with renal failure and in 15 healthy controls. Investigators found that urinary excretion of sugammadex was reduced among participants with renal failure. The median quantity of sugammadex excreted in the urine within 72 hours among participants with renal failure was 29%, and 73% in controls. Nevertheless, one has to conclude on the basis of existing evidence that studies on the use of sugammadex for patients with renal impairment are needed to examine safety, preferably with longer

follow-up than 72 hours, because late renal impairment has to be addressed equally.

Sugammadex has been suspected of increasing the risk of specific adverse effects such as QTc prolongation and bleeding events (Bridion 2014). However, we found limited data from few trials in our systematic review on these variables, and presented data were ineligible for meta-analysis.

The summary of product characteristics provided by Bridion states that the "administration of 4 and 16 mg/kg of Sugammadex in healthy volunteers resulted in maximum and mean prolongations of the aPTT by 17% and 22%, respectively, and PT by 11% and 22%, respectively. These mean aPTT and PT prolongations were limited and of short duration < 30 min" (Bridion 2014). Rahe-Meyer 2014 (n = 1198) included participants undergoing hip or knee surgery and compared sugammadex 4 mg/kg versus usual care (neostigmine or spontaneous recovery). Study findings indicate that sugammadex induced limited (< 8% at 10 minutes) and transient (< 1 hour) increases in activated partial thromboplastin time (aPTT) and prothrombin time (PT) but was not associated with increased risk or severity of bleeding. Tas 2015 (n = 50) investigated the effects of sugammadex and neostigmine on postoperative coagulation parameters and bleeding after seroplasty and demonstrated that sugammadex increased postoperative bleeding without significantly affecting PT and aPTT values. An RCT of healthy adults reported that after administration of sugammadex at doses of 4 mg/kg and 16 mg/kg, a dose-dependent, limited, temporary, and clinically irrelevant prolongation in PT and aPTT was observed (De Kam 2014). A one-year retrospective study (n = 193) performed in participants with high risk of postoperative bleeding (laparotomy for cancer surgery requiring suction drains) did not find sugammadex at doses of 2 and 4 mg·kg^{-1} to be associated with increased bleeding as measured by the amount of blood found in suction drains and dressings (Raft 2011).

However, upon review of the published literature, we are unable to refute or reject any safety concern with regard to sugammadex for patients at high risk of bleeding due to existing severe coagulopathy or due to the nature of procedures associated with high risk of transfusion because evidence is inadequate to support or withhold any use of sugammadex.

We found limited evidence with regard to haemodynamic implications of sugammadex use, but Kizilay 2016 compared the haemodynamic effects of sugammadex and neostigmine in participants with cardiac disease undergoing non-cardiac surgery. Haemodynamic parameters were more prominently increased among participants receiving neostigmine, and cardiac function was noted to be more stable among those given sugammadex. Data show no significant differences between and within groups in terms of QTc values.

Morbidly obese patients make up a high-risk group (Gaszynski 2011), and because of their often compromised respiratory function, they are considered especially vulnerable to residual curarization in the postoperative period influencing respiratory function (Gaszynski 2011). Three trials (n = 161) investigated the optimal sugammadex dose per kilogram body weight; total body weight (TBW) (Foletto 2014), corrected body weight (CBW) (Gaszynski 2011; Georgiou 2013), and ideal body weight (IBW) (Georgiou 2013). All three studies found sugammadex 2 mg/kg to be significantly faster than neostigmine 0.04 to 0.05 mg/kg in reversing neuromuscular blockade at T2 reappearance, and in reducing the risk of postoperative residual curarization (Foletto 2014; Gaszynski 2011).

Researchers have speculated about the influence of volatile anaesthetics and recovery times when neuromuscular blocking agents (NMBAs) are used (Reid 2001). However, we found no significant differences in recovery time to TOFR > 0.9 when anaesthesia maintained with volatile anaesthetic (eight trials; n = 490) was compared with total intravenous anaesthetic (TIVA) (four trials; n = 381) (Analysis 1.2).

Sugammadex was specifically designed to reverse rocuronium as a non-depolarizing NMBA, as is demonstrated by most of the trials included in this review. However, two of the included trials (Lemmens 2010; Rahe-Meyer 2014) used sugammadex to revert vecuronium. Furthermore, Flockton 2008 compared sugammadex following rocuronium versus neostigmine following cisatracurium, and Martini 2014 compared atracurium for induction and mivacurium for maintenance versus rocuronium for both induction and maintenance. Two studies (Castro 2014; Sherman 2014) provided no information on the NMBA used.

Quality of the evidence

This systematic review provides a robust assessment of the efficacy of sugammadex because it includes a large number of trials with large numbers of participants showing a consistent direction of results across all trials and additional confirmation through various exploratory analyses favouring the intervention for our primary outcome.

However, this review also has several potential limitations, as our findings and interpretations are limited by the quality and quantity of available evidence from included RCTs. The RCT is considered the most rigorous method of determining whether a cause-effect relationship exists between an intervention and an outcome. The strength of the RCT lies in the process of randomization, but several potential risks of bias in trial methods can affect results.

The review authors have judged the risk of bias for each included study by using the recommended risk of bias assessment in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). All of our studies had at least one "high or unclear risk of bias", and we considered the risk that trials may overestimate or underestimate the true intervention effect a serious limitation for all trials. In particular, judgements of performance risk of bias and funding risk of bias were overall high. We judged none of the included studies as having low risk of bias.

Application of the GRADE approach enables us to incorporate risk of bias, directness of evidence, heterogeneity, precision of effect estimate, and risk of publication bias.

The GRADE quality of our findings ranks as moderate for our primary outcome, and from low to moderate across different outcomes. The main limiting factors that accounted for decreased quality of evidence included high risk of bias and imprecision (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3).

We mainly assessed the risk of bias of included trials using published data, which ultimately may not reflect the truth. We contacted all trial authors; 12 (33.3%) responded and provided

further information. Lack of reporting of some of the data may have affected our judgement on risk of bias in either direction.

We applied several statistical methods to explore and reduce the extent of bias, such as complete case analysis, trial sequential analysis (TSA), overall methodological bias assessment, and analyses of various relevant clinical and physiological outcomes.

Application of TSA to our primary outcome indicates that at this stage, sugammadex appears superior to neostigmine. TSA provided firm evidence in favour of sugammadex for outcomes such as recovery time from T2 to TOFR > 0.9 minutes, adverse events, and overall signs of postoperative residual paralysis. However, none of the included trials were at low risk of bias, and as TSA cannot be adjusted for risk of bias, we did not calculate the low risk of bias adjusted information size, which ultimately affects the reliability and precision of our findings.

Evaluated outcomes consistently favoured sugammadex. However, we graded the quality of evidence as moderate because of the high proportion of trials at high risk of bias, large clinical and statistical heterogeneity, and small sample sizes, but we upgraded the level of evidence in favour of sugammadex as indicated by TSA analyses.

On the basis of the criteria mentioned above, we deemed the overall GRADE quality of evidence in this review to be moderate.

Sugammadex was specifically designed to reverse rocuronium as a non-depolarizing NMBA, as most of the trials included in this review demonstrated this. However, two of the included trials (Lemmens 2010; Rahe-Meyer 2014) used sugammadex to revert vecuronium.

Potential biases in the review process

We have followed the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* as this official guide describes in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of healthcare interventions (Higgins 2011). We have adhered to this handbook in handling the included RCTs.

Meta-analyses are limited by the quality and quantity of available evidence. Even though our meta-analyses are based on a large quantity of data, results and methods for some of the included studies were not thoroughly described. Furthermore, some of the included trials were not specifically designed to address the primary or secondary outcomes of this review, leading to possibly biased data. We have addressed this problem by labelling studies with high risk of "other bias", as is shown in Characteristics of included studies, Figure 2, and Figure 6, and by downgrading the GRADE quality of evidence (Summary of findings for the main comparison, Summary of findings 2, and Summary of findings 3). Additionally, we are aware that as we have performed many analyses of specific adverse events, the probability of achieving significant results by chance is high.

We used the same search strategy as was used in the original version of this review (Abrishami 2009), and we found 41 eligible studies for inclusion. We cannot exclude the possibility that we may have missed some of the published literature beyond the electronic databases searched for this review. However, the 41 trials with 4206 participants included in this review appear to provide sufficient data for meta-analyses, and our TSAs indicate a better safety profile and clinical superiority of sugammadex compared with neostigmine for the population included in this trial.

We found 20 relevant ongoing trials registered at https://clinicaltrials.gov and three trials awaiting classification, but none of these studies have published data within our main search update from 2008 to 2 May 2016. When published, these trials may change the results and conclusions of this review. However, the main strength of this update consists of the quantity of data comparing sugammadex versus neostigmine in reversing NMB. The new search added eight years of research and 38 new trials to the review that was originally published (Abrishami 2009), which comprised three trials comparing sugammadex and neostigmine. Additionally, we have substantially updated and revised the methods of this review compared with methods of the previous one.

As a consequence, this review diverges from intended adherence to the *Cochrane Handbook for Systematic Reviews of Interventions* by not following the original protocol (Abrishami 2009) prepared for the first version of this review (Abrishami 2009). After several discussions with the editorial team, we made the decision to split the original review in two based on the extensive number of publications using various comparators, interventions, and outcome measures. Therefore, it seemed more appropriate to take the original review in a different direction and place more emphasis on safety issues and efficacy. Although this may be perceived as introduction of post hoc analyses, review authors selected outcomes and subgroup and sensitivity analyses for this review before identifying included trials (search) and extracting data to minimize the risk of bias.

Agreements and disagreements with other studies or reviews

The original published review (Abrishami 2009) found no difference with regard to adverse effects between sugammadex and neostigmine. This review found that sugammadex reduced the risk of adverse events when compared with neostigmine. We updated this review as of 2 May 2016 with regard to the search, adding eight years of research and 38 new trials; the original review (Abrishami 2009) comprised three trials. We re-ran the search on 10 May 2017. Currently three trials are awaiting classification and 20 studies are ongoing.

Our results on the primary outcome, recovery time, are in accordance with the findings of all RCTs included in the meta-analyses, as they reflect superiority for sugammadex as a reversing agent over neostigmine. With regard to our secondary outcomes - risks of adverse and serious adverse events - we found more diverging results among the included trials, although overall risk of adverse events was reduced in the sugammadex group (Analysis 3.1; Analysis 3.5). No previous publication has addressed this issue with the same rigour.

A recent systematic review of sugammadex versus neostigmine for reversal of NMB (Abad-Gurumeta 2015) included 1553 participants across 17 RCTs (all are included in this review).

Abad-Gurumeta 2015 focused mainly on postoperative residual paralysis and drug-related adverse events (Abad-Gurumeta 2015). Review authors found that sugammadex reduced all signs of residual postoperative paralysis (RR 0.46, 95% CI 0.29 to 0.71; P = 0.0004) and risk of minor respiratory events (RR 0.51, 95% CI

0.32 to 0.80; P = 0.0034). However, they reported no differences in critical respiratory events (RR 0.13, 95% CI 0.02 to 1.06; P = 0.06). Sugammadex reduced drug-related adverse effects (RR 0.72, 95% CI 0.54 to 0.95; P = 0.02) but data show no differences in the rate of postoperative nausea or the rate of postoperative vomiting, Findings of this review were generally in line with the results of our updated review with regard to adverse and serious adverse events.

Another systematic review (Paton 2010), which included four trials (n = 606), compared sugammadex versus neostigmine/glycopyrrolate for routine reversal of NMB with economics evaluation. Researchers found that sugammadex was beneficial in terms of enhanced patient safety and increased predictability of recovery from rocuronium-induced NMB, with more efficient use of theatre time and staff. Conclusions of review authors on recovery time, adverse events, and cost-benefit considerations are in line with those of our updated review.

AUTHORS' CONCLUSIONS

Implications for practice

In conclusion, results of this systematic review suggest that, in comparison with neostigmine, sugammadex can more rapidly reverse rocuronium-induced neuromuscular block (NMB) regardless of the depth of the block. Sugammadex 2 mg/kg is 10.22 minutes (˜ 6.6 times) faster in reversing moderate NMB (second twitch (T2)) than neostigmine 0.05 mg/kg (1.96 vs 12.87 minutes), and sugammadex 4 mg/kg is 45.78 minutes (˜ 16.8 times) faster in reversing deep NMB (post-tetanic count (PTC) 1 to 5) when compared with neostigmine 0.07 mg/kg (2.9 vs 48.8 minutes). With number needed to treat for an additional beneficial outcome (NNTB) of eight to avoid an adverse event, sugammadex appears to have a better safety profile than neostigmine when reversing NMB. Patients receiving sugammadex had 40% fewer adverse events than those given neostigmine (risk ratio (RR), specifically risk of bradycardia (RR 0.16, NNTB 14), postoperative nausea and vomiting (RR 0.52, NNTB 16), and overall signs of postoperative residual paralysis (RR 0.40, NNTB 13) were reduced. Both sugammadex and neostigmine were associated with serious adverse events in < 1% of patients, and data show no difference in risk of serious adverse events between groups.

Implications for research

We suggest future trials should include large and adequate sample sizes and low risk of bias to confirm the findings mentioned above, specifically to evaluate the effect of sugammadex on risks of adverse events and serious adverse events, as well as on patient-related outcomes, such as risk of residual NMB and other complications after NMB. More trials are needed to directly establish the efficacy and safety of sugammadex when used in situations such as "cannot intubate, cannot ventilate" and failed intubation during rapid sequence inducing with rocuronium.

ACKNOWLEDGEMENTS

We would like to thank Andrew Smith (Content Editor); Vibeke E Horstmann (Statistical Editor); Jan-Uwe Schreiber and Jeffrey K Lu (Peer Reviewers); Roy Buffery (Consumer Referee); and Jane Cracknell (Managing Editor) for help and editorial advice provided during preparation of this systematic review. We would like to thank Janne Vendt (Information Specialist) and Karen Hovhannisyan (former Trials Search Co-ordinator) for undertaking the electronic searches. We would also like to acknowledge Merck, Sharp and Dohme/Schering-Plough, the manufacturer of sugammadex, and all trial authors who generously provided us with detailed information about trials included in this published systematic review.

REFERENCES

References to studies included in this review

Adamus 2011 *{published and unpublished data}*

Adamus M, Hrabalek L, Wanek T, Gabrhelik T, Zapletalova J. Intraoperative reversal of neuromuscular block with sugammadex or neostigmine during extreme lateral interbody fusion, a novel technique for spine surgery. *Journal of Anesthesia* 2011;**25**(5):716-20. [PUBMED: 21842171]

Balaka 2011 *{published data only (unpublished sought but not used)}*

Balaka C, Poulida S, Miliatou M, Roussakis A, Lavranou V, Moshaki M, et al. Comparison of sugammadex to neostigmine reversal of neuromuscular blockade in patients with myasthenia gravis. Journal of Cardiothoracic and Vascular Anesthesia. 2011; Vol. 25:S22-3. [3275631; http://www.jcvaonline.com/article/S1053-0770(11)00191-1/pdf]

Blobner 2010 *{published and unpublished data}*

Blobner M, Eriksson LI, Scholz J, Motsch J, Della Rocca G, Prins ME. Reversal of rocuronium-induced neuromuscular blockade with sugammadex compared with neostigmine during sevoflurane anaesthesia: results of a randomised, controlled trial. *European Journal of Anaesthesiology* 2010;**27**:874-81. [PUBMED: 20683334]

Brueckmann 2015 *{published and unpublished data}*

Brueckmann B, Sasaki N, Grobara P, Li MK, Woo T, de Bie J, et al. Effects of sugammadex on incidence of postoperative residual neuromuscular blockade: a randomized,controlled study. *British Journal of Anaesthesia* 2015;**115**(5):743-51. [PUBMED: 25935840]

Carron 2013 *{published data only (unpublished sought but not used)}*

Carron M, Veronese S, Foletto M, Ori C. Sugammadex allows fast-track bariatric surgery. *Obesity Surgery* 2013;**23**(10):1558-63. [PUBMED: 23519634]

Castro 2014 *{published data only (unpublished sought but not used)}*

Castro DS Jr, Leão P, Borges S, Gomes L, Pacheco M, Figueiredo P. Sugammadex reduces postoperative pain after laparoscopic bariatric surgery: a randomized trial. *Surgical Laparoscopy Endoscopy & Percutaneous Techniques* 2014;**24**(5):420-3. [PUBMED: 24752165]

Cheong 2015 *{published data only (unpublished sought but not used)}*

Cheong SH, Ki S, Lee J, Lee JH, Kim MH, Hur D, et al. The combination of sugammadex and neostigmine can reduce the dosage of sugammadex during recovery from the moderate neuromuscular blockade. *Korean Journal of Anesthesiology* 2015;**68**(6):547-55. [PUBMED: 26634077]

Flockton 2008 *{published data only (unpublished sought but not used)}*

Flockton EA, Mastronardi P, Hunter JM, Gomar C, Mirakhur RK, Aguilera L, et al. Reversal of rocuronium-induced neuromuscular block with sugammadex is faster than reversal of cisatracurium-induced block with neostigmine. *British Journal of Anaesthesia* 2008;**100**(5):622-30. [PUBMED: 18385265]

Foletto 2014 *{published data only (unpublished sought but not used)}*

Foletto M, Carron M, Zarantonello F, Prevedello L. Respiratory function after sugammadex and neostigmine administration for reversal of moderate rocuronium-induced neuromuscular blockade in morbidly obese patients. 8 ed. Springer New York. Montreal, Canada: 19th World Congress of the International Federation for the Surgery of Obesity and Metabolic Disorders, IFSO 2014, 2014; Vol. 24:1139.

Gaszynski 2011 *{published data only (unpublished sought but not used)}*

Gaszynski T, Szewczyk T, Gaszynski W. Randomized comparison of sugammadex and neostigmine for reversal of rocuronium-induced muscle relaxation in morbidly obese undergoing general anaesthesia. *British Journal of Anaesthesia* 2012;**108**(2):236-9. [PUBMED: 22012861]

Geldner 2012 *{published and unpublished data}*

Geldner G, Niskanen M, Laurila P, Mizikov V, Hubler M, Beck G, et al. A randomised controlled trial comparing sugammadex and neostigmine at different depths of neuromuscular blockade in patients undergoing laparoscopic surgery. *Anaesthesia* 2012;**67**(9):991-8. [PUBMED: 22698066]

Georgiou 2013 *{published data only (unpublished sought but not used)}*

Georgiou P, Zotou A, Siampalioti A, Tagari P, Tsiotsi P, Filos KS. Clinical and cost-effectiveness of Sugammadex versus Neostigmine reversal of Rocuronium-induced neuromuscular block in super obese patients undergoing open laparotomy for bariatric surgery. A randomized controlled trial. European Journal of Anaesthesiology. Barcelona: Euroanesthesia 2013, 2013; Vol. 30:141.

Grintescu 2009 *{published data only (unpublished sought but not used)}*

Grintescu I, Mirea L, Ologoiu D, Ungureanu R, MekauvarS, Vasilescu M. Comparison of the cost effectiveness of sugammadex and neostigmine during general anaesthesia for laparoscopic cholecystectomy. British Journal of Anaesthesia. 2009; Vol. 103, issue 6:917.

Hakimoglu 2016 *{published data only (unpublished sought but not used)}*

Hakimoğlu S, Tuzcu K, Davarcı I, Karcıoğlu M, Ayhan Tuzcu E, Hancı V, et al. Comparison of sugammadex and neostigmine-atropine on intraocular pressure and postoperative effects. *Kaohsiung Journal of Medical Sciences* 2016;**32**(2):80-5. [PUBMED: 26944326]

Illman 2011 *{published data only (unpublished sought but not used)}*

Illman HL, Laurila P, Antila H, Meretoja OA, Alahuhta S, Olkkola KT. The duration of residual neuromuscular block

after administration of neostigmine or sugammadex at two visible twitches during train-of-four monitoring. *Anesthesia and Analgesia* 2011;**112**(1):63-8. [PUBMED: 20978247]

Isik 2016 *{published data only (unpublished sought but not used)}*

Isik Y, Palabiyik O, Cegin BM, Goktas U, Kati I. Effects of sugammadex and neostigmine on renal biomarkers. *Medical Science Monitor* 2016;**22**:803-9. [PUBMED: 26963316]

Jones 2008 *{published and unpublished data}*

* Jones RK, Caldwell JE, Brull SJ, Soto RG. Reversal of profound rocuronium-induced blockade with sugammadex: a randomized comparison with neostigmine. *Anesthesiology* 2008;**109**(5):816–24. [PUBMED: 18946293]

Kaufhold 2016 *{published data only (unpublished sought but not used)}*

Kaufhold N, Schaller SJ, Stäuble CG Baumüller E, Ulm K, Blobner M, et al. Sugammadex and Neostigmine dose-finding study for reversal of residual neuromuscular block at a train-of-four ratio of 0.2 (SUNDRO20). *British Journal of Anaesthesia* 2016;**116**(2):233-40. [PUBMED: 26787792]

Khuenl-Brady 2010 *{published data only (unpublished sought but not used)}*

Khuenl-Brady KS, Wattwil M, Vanacker BF, Lora-Tamayo JI, Rietbergen H, Alvarez-Gómez JA. Sugammadex provides faster reversal of vecuronium-induced neuromuscular blockade compared with neostigmine: a multicenter, randomized, controlled trial. *Anesthesia and Analgesia* 2010;**110**(1):64-73. [PUBMED: 19713265]

Kizilay 2016 *{published and unpublished data}*

Kizilay D, Dal D, Saracoglu KT, Eti Z, Gogus FY. Comparison of neostigmine and sugammadex for hemodynamic parameters in cardiac patients undergoing noncardiac surgery. *Journal of Clinical Anesthesia* 2016;**28**:30-5. [PUBMED: 26796612]

Koc 2015 *{published data only (unpublished sought but not used)}*

Koç F, Turan G, Subaşı D, Ekinci O. Comparison of sugammadex and neostigmine in short term surgery [Turkish: Kısa süreli cerrahide sugammadeks ile neostigminin karşılaştırılması]. *Journal of Clinical and Analytical Medicine* 2015;**6**(1):41-5. [3275673; http://www.jcam.com.tr/files/KATD-1694.pdf]

Kogler 2012 *{published data only (unpublished sought but not used)}*

KoglerJ, Chalfe N, Karaman Ilić M, Hodoba N. Sugammadex reversal of rocuronium-induced neuromuscular block in interventional bronchoscopy procedures: a comparison with neostigmine. European Journal of Anaesthesiology. 2012; Vol. 29:146.

Koyuncu 2015 *{published data only (unpublished sought but not used)}*

Koyuncu O, Turhanoglu S, Ozbakis Akkurt C, Karcıoglu M, Ozkan M, Ozer C, et al. Comparison of sugammadex and conventional reversal on postoperative nausea and vomiting: a randomized, blinded trial. *Journal of Clinical Anesthesia* 2015;**27**(1):51-6. [PUBMED: 25544263]

Kvolik 2012a *{published data only (unpublished sought but not used)}*

Kvolik S, Mraovic B, Kristek J, Stefanic M, Mihaljevic I. Reversal with sugammadex hastens recovery of tracheal reflexes and extubation compared with neostigmine in patients undergoing thyroidectomy. European Journal of Anaesthesiology. 2012; Vol. 29:142.

Kvolik 2012b *{published data only (unpublished sought but not used)}*

Kvolik S, Mraovic B, Kristek J, Stefanic M, Mihaljevic I. Sugammadex does not influence thyroid hormones in the patients undergoing thyroidectomy in propofol anesthesia. European Journal of Anaesthesiology. 2012; Vol. 29:141.

Kvolik 2013 *{published data only (unpublished sought but not used)}*

Kvolik S, Rakipovic A, Mraovic B, Kristek J, Ikic V, Kristic M. Faster increase of BIS registered after the reversal of neuromuscular blockade with sugammadex vs. neostigmine. European Journal of Anaesthesiology. 2013; Vol. 30:40.

Lemmens 2010 *{published data only (unpublished sought but not used)}*

Lemmens HJ, El-Orbany MI, Berry J, Morte JB Jr, Martin G. Reversal of profound vecuronium-induced neuromuscular block under sevofluraneanesthesia: sugammadex versus neostigmine. *BMC Anesthesiology* 2010;**10**:15. [PUBMED: 20809967]

Martini 2014 *{published and unpublished data}*

Martini CH, Boon M, Bevers RF, Aarts LP, Dahan A. Evaluation of surgical conditions during laparoscopic surgery in patients with moderate vs deep neuromuscular block. *British Journal of Anaesthesia* 2014;**112**(3):498-505. [PUBMED: 24240315]

Mekawy 2012 *{published data only (unpublished sought but not used)}*

Mekawy N, Eman A, Ali F. Improved recovery profiles in sinonasal surgery sugammadex: does it have a role?. *Egyptian Journal of Anaesthesia* 2012;**28**(3):175-8. [DOI: 10.1016/j.egja.2011.12.007]

Pongracz 2013 *{published data only (unpublished sought but not used)}*

Pongrácz A, Szatmári S, Nemes R, Fülesdi B, Tassonyi E. Reversal of neuromuscular blockade with sugammadex at the reappearance of four twitches to train-of-four stimulation. *Anesthesiology* 2013;**119**(1):36-42. [PUBMED: 23665915]

Rahe-Meyer 2014 *{published data only (unpublished sought but not used)}*

Rahe-Meyer N, Fennema H, Schulman S, Klimscha W, Przemeck M, Blobner M, et al. Effect of reversal of neuromuscular blockade with sugammadex versus usual care on bleeding risk in a randomized study of surgical patients. *Anesthesiology* 2014;**121**(5):969-77. [PUBMED: 25208233]

Raziel 2013 *{published and unpublished data}*

Raziel A, Messinger G, Sakran N, Szold A, Goitein D. Comparison of two neuromuscular anesthetics reversal in obese patients

undergoing bariatric surgery - a prospective study. 21st International Congress of the European Association for Endoscopic Surgery, EAES. Vienna, Austria, 2013:31.

Riga 2014 *{published and unpublished data}*

Riga M, Batistaki C, Matsota P, Lyrakos G, Zafeiropoulou F, Kostopanagiotou G. Effect of sugammadex versus neostigmine/atropine combination on cognitive function of adult patients after elective surgery: preliminary results. European Journal of Anaesthesiology. 2014; Vol. 31:157-8.

Sabo 2011 *{published data only (unpublished sought but not used)}*

Sabo D, Jones RK, Berry J, Sloan T, Chen JY, Groudine S. Residual neuromuscular blockade at extubation: a randomized comparison of sugammadex and neostigmine reversal of rocuronium-induced blockade in patients undergoing abdominal surgery. *Anesthesia and Clinical Research Journals* 2011;**2**(6):Open assess journal, no pages.

Schaller 2010 *{published data only (unpublished sought but not used)}*

Schaller SJ, Fink H, Ulm K, Blobner M. Sugammadex and neostigmine dose-finding study for reversal of shallow residual neuromuscular block. *Anesthesiology* 2010;**113**(5):1054-60. [DOI: 10.1097/ALN.0b013e3181f4182a; PUBMED: 20885293]

Sherman 2014 *{published data only (unpublished sought but not used)}*

Sherman A, Abelansky Y, Evron S, Ezri T. The effect of sugammadex vs. neostigmine on the postoperative respiratory complications following laparoscopic sleeve gastrectomy. European Journal of Anaesthesiology. 2014; Vol. 31:152.

Sustic 2012 *{published data only}*

Sustic A, Dijana D. Early postoperative gastric emptying in patients undergoing laparoscopic cholecystectomy: sugammadex vs. neostigmine/atropine neuromuscular blockade reversal agents. European Anaesthesiology Congress, EUROANAESTHESIA. Lippincott Williams and Wilkins, 2012; Vol. 29:140.

Tas 2015 *{published data only (unpublished sought but not used)}*

Taş N, Korkmaz H, Yağan Ö, Korkmaz M. Effect of sugammadex on postoperative bleeding and coagulation parameters after septoplasty: a randomized prospective study. *Medical Science Monitor* 2015;**14**:2382-6. [PUBMED: 26271275]

Woo 2013 *{published and unpublished data}*

Woo T, Kim KS, Shim YH, Kim MK, Yoon SM, Lim YJ, et al. Sugammadex versus neostigmine reversal of moderate rocuronium-induced neuromuscular blockade in Korean patients. *Korean Journal of Anesthesiololgy* 2013;**65**(6):501-7. [PUBMED: 24427455]

Wu 2014 *{published data only (unpublished sought but not used)}*

Wu X, Oerding H, Liu J, Vanacker B, Yao S, Dahl V, et al. Rocuronium blockade reversal with sugammadex vs. neostigmine: randomized study in Chinese and Caucasian subjects. *BMC Anesthesiology* 2014;**14**(53):eCollection. [DOI: 10.1186/1471-2253-14-53; PUBMED: 25187755]

Yagan 2015 *{published and unpublished data}*

Yagan O, Karakahya RH, Tas N, Canakci E, Hanci V, Yurtlu BS. Intraocular pressure changes associated with tracheal extubation: comparison of sugammadex with conventional reversal of neuromuscular blockade. *Journal of the Pakistan Medical Assosication* 2015;**65**(11):1219-25. [PUBMED: 26564297]

References to studies excluded from this review

Aho 2012 *{published data only}*

Aho Aj, Kamata K, Yli-Hankala A, Lyytikäinen L-P, Kulkas A, Jäntti V. Elevated BIS and entropy values after sugammadex or neostigmine: an electroencephalographicor electromyographic phenomenon?. *Acta Anaesthesiologica Scandinavica* 2012;**56**(4):465-73. [PUBMED: 22289106]

Baysal 2013 *{published data only}*

Baysal A, Dogukan M, Toman H, Sagiroglu G, Kocak T. The use of sugammadex for reversal of residual blockade after administration of neostigmine and atropine. European Anaesthesiology Congress, EUROANAESTHESIA. Lippincott Williams and Wilkins, 2013; Vol. 30:142.

Dahaba 2012 *{published data only}*

Dahaba AA, Bornemann H, Hopfgartner E, Ohran M, Kocher K, Liebmann M, et al. Effect of sugammadex or neostigmine neuromuscular block reversal on bispectral index monitoring of propofol/remifentanil anaesthesia. *British Journal of Anaesthesia* 2012;**108**(4):602-6. [PUBMED: 22315331]

Gaona 2012 *{published data only}*

Gaona D, Carceles MD, Veiga G, Tedesco M, Motta P. Efficacy and safety of the reversal with sugammadex in deep neuromuscular blockade induced by rocuronium in pediatrics. 15th WFSA World Congress of Anaesthesiologists Predio Ferial de Buenos Aires Argentina. Oxford University Press, 2012; Vol. 108:308-9.

Ghoneim 2015 *{published data only}*

Ghoneim AA, El Beltagy MA. Comparative study between sugammadex and neostigmine in neurosurgical anesthesia in pediatric patients. *Saudi Journal of Anaesthesia* 2015;**9**(3):247-52. [PUBMED: 26240540]

Harazim 2014 *{published data only}*

Harazim H, Stourac P, Seidlova D, Adamus M, Krikava I, Pavlik T. Use of rocuronium and active reversal of neuromuscular blockade with sugammadex in anaesthesia for caesarean section led to reduction of myalgia incidence in early postoperative period: prospective randomised interventional multicentric trial. European Journal of Anaesthesiology. 2014; Vol. 31:194-5.

Kakinuma 2013 *{published data only (unpublished sought but not used)}*

Kakinuma A, Nagatani H, Yasuda A, Yoshimura T, Sawai J, Nakata Y. Combined use of sugammadex and neostigmine for the reversal of rocuronium-induced profound neuromuscular blockade. *Anesthesia and Clinical Research Journal* 2013;**4**(7):337. [DOI: 10.4172/2155-6148.1000337]

Kara 2014 *{published data only}*

Kara T, Ozbagriacik O, Turk HS, Isil CT, Gokuc O, Unsal O, et al. Sugammadex versus neostigmine in pediatric patients: a prospective randomized study. *Revista Brasileira de Anestesiologia* 2014;**64**(6):400-5. [PUBMED: 25437696]

Kzlay 2013 *{published data only (unpublished sought but not used)}*

Kzlay D, Dal D, Saraçoğlu T, Eti Z, Göğüş Y. The effects of sugammadex and neostigmine-atropine administration on hemodynamic parameters in cardiac patients undergoing non-cardiac surgery. European Journal of Anaesthesiology. 2013; Vol. 30:75.

Nagashima 2016 *{published and unpublished data}*

Nagashima S, Takasusuki T, Yamaguchi S, Hamaguchi S. Effects of neostigmine and sugammadex on QT interval and QT dispersion. *Dokkyo Journal of Medical Sciences* 2016;**43**:15-22.

Nagy 2014 *{published data only}*

Nagy HIA, Elkadi HW. Can sugammadex improve the reversal profile of atracurium under sevoflurane anesthesia?. *Egyptian Journal of Anaesthesia* 2014;**30**(1):95-9. [DOI: 10.1016/j.egja.2013.09.007]

NCT03111121 *{unpublished data only}*

NCT03111121. Use of Sugammadex for Reversal of Paralysis in Microlaryngoscopy. https://clinicaltrials.gov/show/NCT03111121, March 23, 2017.

Nemes 2016 *{published and unpublished data}*

Nemes R, Fülesdi B, Pongrácz A, Asztalos L, Szabó-Maák Z, Lengyel S, et al. Impact of reversal strategies on the incidence of postoperative residual paralysis after rocuronium relaxation without neuromuscular monitoring: a partially randomised placebo controlled trial. *European Journal of Anaesthesiology* 2016;**1**:1. [PUBMED: 28030444]

Ozgun 2014 *{published data only}*

Ozgün C, Cakan T, Baltacı B, Başar H. Comparison of reversal and adverse effects of sugammadex and combination of anticholinergic-anticholinesterase agents in pediatric patients. *Journal of Research in Medical Sciences* 2014;**19**(8):762-8. [PUBMED: 25422663]

Pecek 2013 *{published data only}*

* Pecek B, Hollan J, Priman T, Tokic Crnic N, Stankovic V, Polh D. New way of dosing sugammadex for termination of vecuronium induced neuromuscular block. *Zdravniski Vestnik* 2015;**84**:439–46.

Sacan 2007 *{published data only}*

Sacan O, White PF, Tufanogullari B, Klein K. Sugammadex reversal of rocuronium-induced neuromuscular blockade: a comparison with neostigmine-glycopyrrolate and edrophonium-atropine. *Anesthesia and Analgesia* 2007;**104**(3):569-74. [PUBMED: 17312210]

Schepens 2015 *{published data only}*

Schepens T, Cammu G, Saldien V, De Neve N, Jorens PG, Foubert L, et al. Electromyographic activity of the diaphragm during neostigmine or sugammadex-enhanced recovery after neuromuscular blockade with rocuronium: a randomised controlled study in healthy volunteers. *European Journal of Anaesthesiology* 2015;**32**(1):49-57. [PUBMED: 25111539]

Stourac 2016 *{published and unpublished data}*

Stourac P, Adamus M, Seidlova D, Pavlik T, Janku P, Krikava I, et al. Low-dose or high-dose rocuronium reversed with neostigmine or sugammadex for cesarean delivery anesthesia: a randomized controlled noninferiority trial of time to tracheal intubation and extubation. *Anesthesia and Analgesia* 2016;**122**(5):1536-45. [DOI: 10.1213/ANE.0000000000001197; PUBMED: 26974018]

Veiga Ruiz 2011 *{published data only}*

Veiga Ruiz G, Carceles Baron MD, Dominguez Serrano N, Lopez Fuentes L, Orozco Montes J, Alvarez-Gomez JA. Sugammadex reversal efficacy and security vs neostigmine in the rocuronium-induced neuromuscular blockade in paediatric patients. European Journal of Anaesthesiology. Abstracts and Programme: EUROANAESTHESIA 2011: The European Anaesthesiology Congress: Paediatric Anaesthesia and Intensive Care, 2011; Vol. 28:153.

References to studies awaiting assessment

Kim 2016 *{published data only}*

Kim K, Oh Y, Kim T, Oh S, Sin Y. Relationship between first-twitch depression and train-of-four ratio during sugammadex reversal of rocuronium-induced neuromuscular blockade. *Korean Journal of Anesthesiology* 2016;**1**:1. [PUBMED: 27274368]

NCT02243943 *{unpublished data only}*

NCT02243943. Effect of Neuromuscular Reversal With Sugammadex on Postoperative Recovery Profile (Neuropa). https://clinicaltrials.gov/show/NCT02243943, September 12, 2014.

Sen 2016 *{unpublished data only}*

Sen A, Erdivanli B, Tomak Y, Pergel A. Reversal of neuromuscular blockade with sugammadex or neostigmine/atropine: effect on postoperative gastrointestinal motility. *Journal of Clinical Anesthesia* 2016;**1**:1. [PUBMED: 27290978]

References to ongoing studies

NCT01539044 *{unpublished data only}*

NCT01539044. Optimal Relaxation Technique for Laparotomies With Rocuronium Infusion Followed by Sugammadex Reversal (ProjectO5Rs). https://clinicaltrials.gov/show/NCT01539044, February 15, 2012.

NCT01748643 *{unpublished data only}*

NCT01748643. CURES: The Effect of Deep Curarisation and Reversal With Sugammadex on Surgical Conditions and Perioperative Morbidity (CURES). https://clinicaltrials.gov/show/NCT01748643, December 6, 2012.

NCT02160223 *{unpublished data only}*

NCT02160223. Sugammadex Compared With Neostigmin/Atropin for Neuromuscular Block Reversal in Patients With Obstructive Sleep Apnea. https://clinicaltrials.gov/show/NCT02160223, June 8, 2014.

NCT02256280 *{unpublished data only}*

NCT02256280. A Randomized Double Blind Controlled Trial Comparing Sugammadex and Neostigmine After Thoracic Anesthesia (DATA). https://clinicaltrials.gov/show/NCT02256280, September 24, 2014.

NCT02330172 *{unpublished data only}*

NCT02330172. Sugammadex Provide Better Surgical Condition Compared With Neostigmine in Laryngeal Microsurgery. https://clinicaltrials.gov/show/NCT02330172, December 9, 2014.

NCT02361060 *{unpublished data only}*

NCT02361060. Effects of Neuromuscular Block Reversal With Sugammadex vs Neostigmine on Postoperative Respiratory Outcomes After Major Abdominal Surgery. https://clinicaltrials.gov/show/NCT02361060, December 23, 2014.

NCT02414880 *{unpublished data only}*

NCT02414880. Sugammadex Versus Neostigmine in Patients With Liver Cirrhosis Undergoing Liver Resection. https://clinicaltrials.gov/show/NCT02414880, April 5, 2015.

NCT02454504 *{unpublished data only}*

NCT02454504. Quality of Awakening and Impact on Cognitive Function After Administration of Sugammadex in Robotic Radical Cystectomy. https://clinicaltrials.gov/show/NCT02454504, May 6, 2015.

NCT02648503 *{unpublished data only}*

NCT02648503. Deep Neuromuscular Block and Sugammadex Versus Standard of Care on Quality of Recovery in Patients Undergoing Elective Laparoscopic Cholecystectomy. https://clinicaltrials.gov/show/NCT02648503, December 7, 2015.

NCT02666014 *{unpublished data only}*

NCT02666014. Sugammadex Versus Neostigmine for Postoperative Nausea and Vomiting After Laparoscopic Gynaecological Surgery. https://clinicaltrials.gov/show/NCT02666014, February 2, 2015.

NCT02697929 *{unpublished data only}*

NCT02697929. Sugammadex/Neostigmine and Liver Transplantation. https://clinicaltrials.gov/show/NCT02697929, February 13, 2016.

NCT02698969 *{unpublished data only}*

NCT02698969. Recovery of Muscle Function After Deep Neuromuscular Block by Means of Diaphragm Ultrasonography. https://clinicaltrials.gov/show/NCT02698969, February 15, 2016.

NCT02845375 *{unpublished data only}*

NCT02845375. Effect of Neuromuscular Blockade and Reversal on Breathing (BREATH). https://clinicaltrials.gov/show/NCT02845375, July 14, 2016.

NCT02860507 *{unpublished data only}*

NCT02860507. Study to Determine if Administration of Sugammadex Impacts Hospital Efficiency. https://clinicaltrials.gov/show/NCT02860507, August 2, 2016.

NCT02861131 *{unpublished data only}*

NCT02861131. The Effect of Sugammadex Versus Neostigmine on Postoperative Pulmonary Complications. https://clinicaltrials.gov/show/NCT02861131, July 14, 2016.

NCT02909439 *{unpublished data only}*

NCT02909439. Quality of Recovery After Reversal With Neostigmine or Sugammadex. https://clinicaltrials.gov/show/NCT02909439, August 31, 2016.

NCT02939430 *{unpublished data only}*

NCT02939430. Sugammadex Reversal of Neuromuscular Blockade and Postoperative Bleeding (Suga_bleeding). https://clinicaltrials.gov/show/NCT02939430, October 17, 2016.

NCT03108989 *{unpublished data only}*

NCT03108989. Comparison the Postoperative Quality of Recovery Between Neostigmine and Sugammadex in Elderly Patients Undergoing Trans Pars Plana Vitrectomy With General Anesthesia - Randomized Controlled Trial. https://clinicaltrials.gov/show/NCT03108989, April 6, 2017.

NCT03116997 *{unpublished data only}*

NCT03116997. Study of Recovery of Strength After Surgery Comparing Two Different Medications for Reversal of Muscle Relaxant. https://clinicaltrials.gov/show/NCT03116997, April 12, 2017.

NCT03144453 *{unpublished data only}*

NCT03144453. Recovery From Anesthesia After Robotic Assisted Radical Cystectomy. https://clinicaltrials.gov/show/NCT03144453, May 3, 2017.

Additional references

Abad-Gurumeta 2015

Abad-Gurumeta A, Ripollés-Melchor J, Casans-Francés R, Espinosa A, Martínez-Hurtado E, Fernández-Pérez C, et al. A systematic review of sugammadex vs neostigmine for reversal of neuromuscular blockade. *Anaesthesia* 2015;**70**(12):1441-52. [PUBMED: 26558858]

Agrell 1998

Agrell B, Dehlin O. The clock-drawing test. *Age and Aging* 1998;**27**:399-403. [PUBMED: 23144287]

Ali 1970

Ali HH, Utting JE, Gray C. Stimulus frequency in the detection of neuromuscular block in humans. *British Journal of Anaesthesia* 1970;**42**(11):967-78. [PUBMED: 5488360]

Ali 1971

Ali HH, Utting JE, Gray TC. Quantitative assessment of residual antidepolarizing block II. *British Journal of Anaesthesia* 1971;**43**(5):478-85. [PUBMED: 4254032]

Altman 2003

Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003;**326**(7382):219. [PUBMED: 12543843]

Appelbaum 2003

Appelbaum R, Mulder R, Saddler J, Kopman AF, McShane AJ. Atracurium associated with postoperative residual curarization (multiple letters). *British Journal of Anaesthesia* 2003;**90**(4):523-4.

Arbous 2005

Arbous MS, Meursing AE, van Kleef JW, de Lange JJ, Spoormans HH, Touw P, et al. Impact of anaesthesia management characteristics on severe morbidity and mortality. *Anesthesiology* 2005;**102**(2):257-68. [PUBMED: 15681938]

Baillard 2005

Baillard C, Clec'h C, Catineau J, Salhi F, Gehan G, Cupa M, et al. Postoperative residual neuromuscular block: a survey of management. *British Journal of Anaesthesia* 2005;**95**(5):622-6. [PUBMED: 16183681]

Berg 1997

Berg H, Roed J, Viby-Mogensen J, Mortensen CR, Engbaek J, Skovgaard LT, et al. Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. *Acta Anaesthesiologica Scandinavica* 1997;**41**(9):1095-103. [PUBMED: 9366929]

Bevan 1988

Bevan DR, Smith CE, Donati F. Postoperative neuromuscular blockade: a comparison between atracurium, vecuronium and pancuronium. *Anesthesiology* 1988;**69**(2):272-6. [PUBMED: 2900612]

Bevan 1996

Bevan DR, Kahwaji R, Ansermino JM, Reimer E, Smith MF, O'Connar GA, et al. Residual block after mivacurium with or without edrophonium reversal in adults and children. *Anesthesiology* 1996;**84**(2):362-7. [PUBMED: 8602667]

Bowman 2006

Bowman WC. Neuromuscular block. *British Journal of Pharmacology* 2006;**147**(Suppl 1):S277-86. [PUBMED: 16402115]

Bridion 2014

http://www.ema.europa.eu/. Summary of Product Characteristics of BRIDION. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000885/WC500052310.pdf.

Brok 2009

Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive - Trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *Journal of Clinical Epidemiology* 2009;**38**(1):287-98. [PUBMED: 18824466]

Brull 1991

Brull SJ, Ehrenwerth J, Connelly NR, Silverman DG. Assessment of residual curarization using low-current stimulation. *Canadian Journal of Anaesthesia* 1991;**38**(2):164-8. [PUBMED: 1673643]

Caldwell 2009

Caldwell JE. Clinical limitations of acetylcholinesterase antagonists. *Journal of Critical Care* 2009;**24**(1):21-8. [PUBMED: 19272535]

Chan 2004

Chan AW, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA* 2004;**291**(20):2457-65. [PUBMED: 15161896]

de Boer 2007

de Boer HD, Driessen JJ, Marcus MA, Kerkkamp H, Heeringa M, Klimek M. Reversal of rocuronium-induced (1.2mg/kg) profound neuromuscular block by sugammadex: a multicenter, dose-finding and safety study. *Anesthesiology* 2007;**107**(2):239-44. [PUBMED: 17667567]

De Kam 2014

De Kam PJ, Kruithof AC, van Lierop MJ, Moerland M, Dennie J, Troyer MD, et al. Lack of a clinically relevant effect of sugammadex on anti-Xa activity or activated partial thromboplastin time following pretreatment with either unfractionated or low-molecular-weight heparin in healthy subjects. *International Journal of Clinical Pharmacology and Therapeutics* 2014;**52**(8):631-41. [PUBMED: 24800921]

Debaene 2003

Debaene B, Plaud B, Dilly MP, Donati F. Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. *Anesthesiology* 2003;**98**:1042-8. [PUBMED: 12717123]

Dexter 1995

Dexter F, Coffin S, Tinker JH. Decreases in anesthesia-controlled time cannot permit one additional surgical operation to be reliably scheduled during the workday. [Decreases in anesthesia-controlled time cannot permit one additional surgical operation to be reliably scheduled during the workday]. *Anesthesia & Analgesia* 1995;**81**(6):1263-8. [PUBMED: 7486114]

Drugs.com

Generic Bridion availability. www.drugs.com. [www.drugs.com/availability/generic-bridion.html]

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34. [PUBMED: 9310563]

Eikermann 2006

Eikermann M, Blobner M, Groeben H, Rex C, Grote T, Neuhäuser M, et al. Postoperative upper airway obstruction after recovery of the train of four ratio of the adductor pollicis muscle from neuromuscular blockade. *Anesthesia and Analgesia* 2006;**102**(3):937-42. [PUBMED: 16492855]

Eriksson 1993

Eriksson LI, Sato M, Severinghaus JW. Effect of vecuronium-induced partial neuromuscular block on hypoxic ventilatory response. *Anesthesiology* 1993;**78**(4):693-9. [PUBMED: 8096684]

Eriksson 1997

Eriksson LI, Sundman E, Olsson R, Nilsson L, Witt H, Ekberg O, et al. Functional assessment of the pharynx at rest and during swallowing in partially paralysed humans. Simultaneous video manometry and mechanomyography of awake human volunteers. *Anesthesiology* 1997;**87**(5):1035-43. [PUBMED: 9366453]

Fawcett 1995

Fawcett WJ, Dash A, Francis GA, Liban JB, Cashman JN. Recovery from neuromuscular blockade: residual curarization following atracurium or vecuronium by bolus dosing or infusions. *Acta Anaesthesiologica Scandinavica* 1995;**39**(3):288-93. [PUBMED: 7793202]

Fuchs-Buder 2012

Fuchs-Buder T, Meistelman C, Schreiber JU. Is sugammadex economically viable for routine use. *Current Opinions in Anesthesiology* 2012;**25**(2):217-20. [PUBMED: 22157200]

Gijsenbergh 2005

Gijsenberg F, Ramael S, Houwing N, van Lersel T. First human exposure of Org 25969, a novel agent to reverse the action of rocuronium bromide. *Anesthesiology* 2007;**103**(4):695-703. [PUBMED: 16192761]

Golembiewski 2016

Golembiewski J. Sugammadex. *Journal of PeriAnesthesia Nursing* 2016;**31**(4):354-7. [PUBMED: 27444769]

GradePro software [Computer program]

gradepro.org. GRADEpro GDT. Version Accessed December 2016. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Hayes 2001

Hayes AH, Mirakyr RK, Brestin DS, Reid JE, McCourt KC. Postoperative residual block after intermediate acting neuromuscular blocking drugs. *Anaesthesia* 2001;**56**(4):312-8. [PUBMED: 11284816]

Higgins 2011

Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. handbook.cochrane.org.

Hozo 2005

Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *British Medical Research Methodology* 2005;**5**(13):1-10. [DOI: 10.1186/1471-2288-5-13; PUBMED: 15840177]

Hutton 2000

Hutton JL, Williamson PR. Bias in meta-analysis due to outcome variable selection within studies. *Journal of the Royal Statistical Society Series C* 2000;**49**:359-70. [DOI: 10.1111/1467-9876.00197]

Insinga 2016

Insinga RP, Joyal C, Goyette A, Galarneau A. A discrete event simulation model of clinical and operating room efficiency outcomes of sugammadex versus neostigmine for neuromuscular block reversal in Canada. *BMC Anesthesiology* 2016;**16**(1):114. [PUBMED: 7852231]

Jensen 1988

Jensen E, Viby-Mogensen J, Bang U. The Accelograph: a new neuromuscular transmission monitor. *Acta Anaesthesiologica Scandinavica* 1988;**32**(1):49-52. [PUBMED: 2830761]

Keating 2016

Keating GM. Sugammadex: a review of neuromuscular blockade reversal. *Drugs* 2016;**76**(10):1041-52. [PUBMED: 27324403]

Kim 2002

Kim KS, Lew SH, Cho HY, Cheong MA. Residual paralysis induced by either vecuronium or rocuronium after reversal with pyridostigmine. *Anesthesia and Analgesia* 2002;**95**(6):1656-60. [PUBMED: 12456433]

Lan 1983

Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983;**70**(3):659-63. [DOI: 10.1093/biomet/70.3.659]

Ledowski 2012

Ledowski T, Hillyard S, Kozman A, Johnston F, Gillies E, Greenaway M, et al. Unrestricted access to sugammadex: impact on neuromuscular blocking agent choice, reversal practice and associated healthcare costs. *Anesthesia and Intensive Care Journal* 2012;**40**(2):340-3. [PUBMED: 22417031]

Maybauer 2007

Maybauer DM, Geldner G, Blobner M, Puhringer F, Hofmockel R, Rex C, et al. Incidence and duration of residual paralysis at the end of surgery after multiple administrations of cisatracurium and rocuronium. *Anaesthesia* 2007;**62**(1):12-7. [PUBMED: 17156221]

McCaul 2002

McCaul C, Tobin E, Boylan JF, McShane AJ. Atracurium is associated with postoperative residual curarization. *British Journal of Anaesthesia* 2002;**89**(5):766-9. [PUBMED: 12393778]

Mirakhur 1985

Mirakhur RK. Antagonism of the muscarinic effects of edrophonium with atropine or glycopyrrolate. A comparative study. *British Journal of Anaesthesia* 1985;**57**(12):1213-6. [PUBMED: 4084429]

Murphy 2006

Murphy GS. Residual neuromuscular blockade: incidence, assessment, and relevance in the postoperative period. *Minerva Anestesiologica* 2006;**72**(3):97-109. [PUBMED: 16493386]

Murphy 2008

Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS. Residual neuromuscular blockade and critical

respiratory events in the postanesthesia care unit. *Anesthesia and Analgesia* 2008;**107**(1):130-7. [PUBMED: 18635478]

Murphy 2010

Murphy GS, Brull SJ. Residual neuromuscular block: lessons unlearned. Part I. Definitions, Incidence, and adverse physiologic effects of residual neuromuscular block. *Anesthesia and Analgesia* 2010;**111**(1):120-8. [PUBMED: 20442260]

Murphy 2011

Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Marymont JH, Vender JS, et al. Intraoperative acceleromyography monitoring reduces symptoms of muscle weakness and improves quality of recovery in the early postoperative period. *Anesthesiology* 2011;**115**(5):946-54. [PUBMED: 21946094]

Murphy 2013

Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Shear T, Vender JS, et al. Postoperative residual neuromuscular blockade is associated with impaired clinical recovery. *Anesthesia and Analgesia* 2013;**117**(1):133-41. [PUBMED: 23337416]

Naguib 2009

Naguib M, Brull SJ. Sugammadex: a novel selective relaxant binding agent. *Expert Review of Clinical Pharmacology* 2009;**2**(1):37-53. [PUBMED: 24422770]

Park 2015

Park JY. Benefits and risks of sugammadex. *Korean Journal of Anesthesiology* 2015;**68**(1):1-2. [PUBMED: 25664147]

Paton 2010

Paton F, Paulden M, Chambers D, Heirs M, Duffy S, Hunter JM, et al. Sugammadex compared with neostigmine/glycopyrrolate for routine reversal of neuromuscular block: a systematic review and economic evaluation. *British Journal of Anaesthesia* 2010;**105**(5):558-67. [PUBMED: 20935005]

Pedersen 1994

Pedersen T. Complications and death following anaesthesia. A prospective study with special reference to the influence of patient-, anaesthesia-, and surgery-related risk factors. *Danish Medical Bulletin* 1994;**41**(3):319-31. [PUBMED: 7924461]

Plaud 2010

Plaud B, Debaene B, Donati F, Marty J. Residual paralysis after emergence from anesthesia. *Anesthesiology* 2010;**112**(4):1013-22. [PUBMED: 20234315]

Pogue 1997

Pogue JM, Yusuf S. Cumulating evidence from randomized trials: utilizing sequential monitoring boundaries for cumulative meta-analysis. *Controlled Clinical Trials* 1997;**18**(6):580-93. [PUBMED: 9408720]

Pogue 1998

Pogue J, Yusuf S. Overcoming the limitations of current meta-analysis of randomised controlled trials. *Lancet* 1998;**351**(9095):45-52. [PUBMED: 9433436]

PubChem 2016

National Center for Biotechnology Information. Rocuronium. PubChem Compound Database 2016. [https://pubchem.ncbi.nlm.nih.gov/compound/441290]

Raft 2011

Raft J, Betala Belinga JF, Jurkolow G, Desandes E, Longrois D, Meistelman C. Clinical evaluation of post-surgical bleeding after a sugammadex injection. *Annales Françaises d'Anesthésie et de Réanimation* 2011;**30**(10):714-7. [PUBMED: 21741200]

Reid 2001

Reid JE, Breslin DS, Mirakhur RK, Hayes AH. Neostigmine antagonism of rocuronium block during anesthesia with sevoflurane, isoflurane or propofol. *Canadian Journal of Anesthesia* 2001;**48**(4):351-5. [PUBMED: 11339776]

RevMan 5.3.5 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan) Version 5.3.5. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2015.

Sauer 2011

Sauer M, Stahn A, Soltesz S, Noeldge-Schomburg G, Mencke T. The influence of residual neuromuscular block on the incidence of critical respiratory events. A randomised, prospective, placebo-controlled trial. *European Journal of Anaesthesiology* 2011;**28**(12):842-8. [PUBMED: 21455074]

Shorten 1993

Shorten GD. Postoperative residual curarization: incidence, aetiology and associated morbidity. *Anaesthesia and Intensive Care* 1993;**21**(6):782-9. [PUBMED: 8122734]

Sorgenfrei 2006

Sorgenfrei IF, Norrild K, Larsen PB, Stensballe J, Ostergaard D, Prins ME, et al. Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex, a dose-finding and safety study. *Anesthesiology* 2006;**104**(4):667-74. [PUBMED: 16571960]

Sparr 2007

Sparr HJ, Vermeyen KM, Beaufort AM, Rietbergen H, Proost JH, Saldien V, et al. Early reversal of profound rocuronium-induced neuromuscular blockade by sugammadex in a randomised multicenter study: efficacy, safety, and pharmacokinetics. *Anesthesiology* 2007;**106**(5):935-43. [PUBMED: 17457124]

Staals 2010

Staals LM, Snoeck MM, Driessen JJ, van Hamersvelt HW, Flockton EA, van den Heuvel MW, et al. Reduced clearance of rocuronium and sugammadex in patients with severe to end-stage renal failure: a pharmacokinetic study. *British Journal of Anaesthesia* 2010;**104**(1):31-9. [PUBMED: 20007792]

Sundman 2000

Sundman E, Witt H, Olsson R, Ekberg O, Kuylenstierna R, Eriksson LI. The incidence and mechanisms of pharyngeal and upper oesophageal dysfunction in partially paralysed humans. Pharyngeal video radiography and simultaneous manometry

after atracurium. *Anesthesiology* 2000;**92**(4):977-84. [PUBMED: 10754616]

Thorlund 2009

Thorlund K, Devereaux PJ, Wetterslev J, Guyatt G, Ioannidis JP, Thabane L, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses?. *International Journal of Epidemiology* 2009;**38**(1):276-86. [PUBMED: 18824467]

Tombaugh 1992

Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *Journal of the American Geriatric Society* 1992;**40**(9):922-35. [PUBMED: 1512391]

Tramer 1999

Tramer MR, Fuchs-Buder T. Omitting antagonism of neuromuscular block: effect on postoperative nausea and vomiting and risk of residual paralysis. A systematic review. *British Journal of Anaesthesia* 1999;**82**(3):379-86. [PUBMED: 10434820]

Viby-Mogensen 1979

Viby-Mogensen J, Jørgensen BC, Ording H. Residual curarization in the recovery room. *Anesthesiology* 1979;**50**(6):539-41. [PUBMED: 156513]

Viby-Mogensen 1981

Viby-Mogensen J, Howardy-Hansen P, Chraemmer-Jørgensen B, Ording H, Engbaek J, Nielsen A. Posttetanic count (PTC): a new method of evaluating an intense nondepolarizing neuromuscular blockade. *Anesthesiology* 1981;**55**(4):458-61. [PUBMED: 7294384]

Viby-Mogensen 1988

Viby-Mogensen J, Jensen E, Werner M, Nielsen HK. Measurement of acceleration: a new method of monitoring neuromuscular function. *Acta Anaesthesiologica Scandinavica* 1988;**32**(1):45-8. [PUBMED: 2830760]

Viby-Mogensen 2000

Viby-Mogensen J. Postoperative residual curarization and evidence-based anaesthesia. *British Journal of Anaesthesia* 2000;**84**(3):301-3. [PUBMED: 10793585]

Wetterslev 2008

Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *Journal of Clinical Epidemiology* 2008;**61**(1):64-75. [PUBMED: 18083463]

Wetterslev 2009

Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Medical Research Methodology* 2009;**9**:86. [PUBMED: 20042080]

www.fda.gov

Highligts of prescribing information: BLOXIVERZ™ (neostigmine methylsulfate). www.fda.gov. [https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204078s000lbl.pdf]

References to other published versions of this review

Abrishami 2008

Abrishami A, Ho J, Wong J, Yin L, Chung F. Sugammadex, a selective reversal medication for preventing postoperative residual neuromuscular blockade. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD007362]

Abrishami 2009

Abrishami A, Ho J, Wong J, Yin L, Chung F. Sugammadex, a selective reversal medication for preventing postoperative residual neuromuscular blockade. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007362.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adamus 2011

Methods	**Study design:** randomized, controlled trial **Sample size calculation:** powered to detect a significant difference of 6 minutes or longer in recovery time from injection of sugammadex or neostigmine to TOFR > 0.9
Participants	**Number of randomized participants:** 22 **Inclusion criteria:** patients scheduled for XLIF (extreme lateral interbody fusion) under general anaesthesia requiring tracheal intubation **Exclusion criteria:** ASA > II; expected difficult tracheal intubation and contraindication to drugs used in the study; using medication known to interfere with NMBAs; having severe renal, hepatic, metabolic, or neuromuscular disease

Adamus 2011 *(Continued)*

Interventions	**Anaesthesia:** induction with midazolam (1 to 2 mg), sufentanil (0.2 to 0.3 µg/kg), and propofol (2 mg/kg); anaesthesia maintained with SEVO to MAC 1. Boluses of sufentanil 5 to 10 µg administered when necessary **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 2.5 mg **Comparison:** sugammadex 2 mg/kg (n = 11) vs neostigmine 0.04 mg/kg + atropine 0.02 mg/kg (n = 11) **Administration time of sugammadex or neostigmine:** reappearance of T2
Outcomes	**Main objective:** To determine the extent to which NMB must be reversed for reliable identification of lumbar nerve roots **Secondary objective:** time course of reversal after sugammadex or neostigmine
Notes	**Publication type:** peer-reviewed article **Country:** Czech Republic **Conversions:** Median + Range to Mean + SD following guidelines from Hozo 2005 **Handling of adverse events:** no discrepancy between AEs presented in the original article and AEs presented in this review **Authors' conclusions:** Intraoperative reversal of shallow rocuronium-induced block with sugammadex or neostigmine is an efficient method. For reliable detection of lumbar nerve roots with a stimulating current of 10 mA, the block should be reversed to a TOFR ≥ 0.70. For current intensity of 5 mA, TOFR should reach 0.90 **Contact:** first trial author Milan Adamus contacted by email: milan.adamus@seznam.cz; replied * Indicates unpublished data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers with block-wise randomization
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque, sealed envelopes*
Blinding of participants (performance bias)	Low risk	Participants were under general anaesthesia and therefore were blinded*
Blinding of personnel (performance bias)	High risk	Surgeon was blinded to the reversal drug used for a particular participant at the beginning of the study; however, because differences in the onset of effect between sugammadex and neostigmine were substantial, he/she gradually learned to guess which was injected. Anaesthesiologist was not blinded
Blinding of primary outcome assessment (detection bias)	High risk	Anaesthesiologist was the TOF-watch assessor and was not blinded
Blinding of safety assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	22 patients were enrolled in the study, and reliable NMT monitoring was set up for all of them. However, for 1 patient in the neostigmine group, the appropriate lumbar nerve roots were not identified despite full recovery from NMB

Adamus 2011 *(Continued)*

		(TOFR = 0.99). This patient was excluded from the study. Resulting groups consisted of 11 and 10 participants in the sugammadex and neostigmine groups, respectively
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published article clearly includes all expected outcomes
Funding bias	High risk	Conflict of interest: Milan Adamus is a member of the advisory board of MSD (Schering-Plough, s.r.o., a subsidiary of Merck & Co., Inc.) and has received lecture honoraria from MSD. This study received no financial support from MSD
Other bias	Low risk	Appears free of other sources of bias. Study sample size calculation designed to address this review's primary outcome. No significant differences between groups regarding age, gender, weight, height, BMI, and ASA scores

Balaka 2011

Methods	**Study design:** randomized, prospective study **Sample-size calculation:** no information available
Participants	**Number of randomized participants:** 40 **Inclusion criteria:** aged 18 to 63, with myasthenia gravis (MG) - Osserman's classification I to III and Leventhal score < 10 points, ASA physical status I to III, undergoing transsternal thymectomy **Exclusion criteria:** no information available
Interventions	**Anaesthesia:** no information available **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 0.15 mg/kg **Comparison:** sugammadex 4.0 mg/kg (n = 20) vs neostigmine 2.5 mg (n = 20) **Administration time of sugammadex or neostigmine:** TOF ~ 50%
Outcomes	Recovery time from TOF ~ 50% to TOF > 90%, signs of residual NMB
Notes	**Publication type:** meeting abstract **Country:** Greece **Conversions:** none **Handling of adverse events:** No discrepancy exists between AEs presented in the original article and in this review **Authors' conclusions:** Sugammadex seems to be superior to neostigmine as a reversal agent of rocuronium-induced intense NMB, leading to a more rapid reappearance of normal muscle activity in these patients with their highly increased sensitivity to non-depolarizing neuromuscular blocking drugs **Contact:** first trial author Christina Balaka contacted by email: christinabalaka@yahoo.com on 30.09.2015; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement

Balaka 2011 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Divided randomly"; no further information available
Allocation concealment (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of participants (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of personnel (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of primary outcome assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of safety assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to assess owing to insufficient information
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published meeting abstract clearly includes all expected outcomes
Funding bias	Unclear risk	Unable to assess owing to insufficient information
Other bias	Unclear risk	Unable to assess owing to insufficient information

Blobner 2010

Methods	**Study design:** phase 3A, European, 13-centre, randomized, parallel-group, comparative, active-controlled, safety assessor-blinded trial (the AURORA trial) **Sample size calculation:** powered to detect a difference ≥ 5 minutes from start of administration of sugammadex/neostigmine to TOFR > 0.9 between treatment groups
Participants	**Number of randomized participants:** 98 **Inclusion criteria:** ASA I to III, age ≥ 18 and of any body weight, scheduled for an elective surgical procedure under general anaesthesia **Exclusion criteria:** expected difficult intubation; receiving medication known to interact with rocuronium or vecuronium; having neuromuscular or significant renal disease, a history of malignant hyperthermia, an allergy, or other contraindication to medications used during the study; pregnant, potentially pregnant, or breastfeeding
Interventions	**Anaesthesia:** induced with propofol and maintained with sevoflurane **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 0.1 to 0.2 mg/kg **Comparison:** sugammadex 2.0 mg/kg (n = 49) vs neostigmine 50 µg/kg plus glycopyrrolate 10 µg/kg (n = 49) **Administration time of sugammadex or neostigmine:** reappearance of T2

Blobner 2010 *(Continued)*

Outcomes	**Primary endpoint:** time from start of administration of sugammadex/neostigmine to TOFR > 0.9 **Secondary endpoint:** time from start of administration of sugammadex/neostigmine to TOFR > 0.8 and 0.7 **Other efficacy analysis:** assessment of clinical signs of recovery (level of consciousness, 5 second head-lift, general muscle weakness) **Safety analysis:** adverse events, serious adverse events, heart rate, blood pressure
Notes	**Publication type:** peer-reviewed article **Country:** European study, 13 centres **Conversions:** Median + Range to Mean + SD following guidelines from Hozo 2005 **Handling of adverse events:** Data presented in Table 2 - "Summary of the clinical signs of recovery and level of consciousness" - regarding number of participants with muscle weakness and number of participants not able to perform 5 second head-lift were considered to be adverse events in this review and were counted as such. Furthermore, study authors provided more detailed information regarding adverse events through email correspondence **Authors' conclusions:** Recovery of neuromuscular function after rocuronium to a TOFR = 0.9 is on average about 13 times faster with 2 mg/kg sugammadex than with 50 µg/kg neostigmine. Even more important, 98% of participants were sufficiently recovered within 5 minutes after sugammadex but 100 minutes after neostigmine before 98% of participants were sufficiently recovered. The safety profile did not differ between sugammadex-treated and neostigmine-treated patients **Contact:** First trial author Manfred Blobner contacted by email: blobner@lrz.tum.de; replied to questions regarding blinding of outcome assessor and referred to Tiffany Woo about questions regarding adverse events; replied 29.03.16 * Indicates unpublished data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization codes were entered into a central randomization system - part of a secured trial website. Enrolled participants were given a number in sequence of their enrolment and received a treatment code using the randomization system
Allocation concealment (selection bias)	Low risk	Central allocation (secondary to central randomization)
Blinding of participants (performance bias)	High risk	Open-label study
Blinding of personnel (performance bias)	High risk	Open-label study
Blinding of primary outcome assessment (detection bias)	Low risk	TOF-watch assessor was blinded to treatment assignment*
Blinding of safety assessment (detection bias)	Low risk	Safety assessor was blinded to treatment assignment
Incomplete outcome data (attrition bias)	Low risk	All participants are accounted for, and missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data

Blobner 2010 *(Continued)*

All outcomes		across groups: 98 participants were enrolled - 49 in the sugammadex group and 49 in the neostigmine group. One participant in each group did not receive study drug, and the all-patients-treated population included 48 participants in each group. All of these had ≥ 1 postbaseline efficacy measurement and, therefore, made up the intention-to-treat population
Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrials.gov (NCT00451217); all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way
Funding bias	High risk	This work was supported by MSD, Oss, The Netherlands. M.B. and J.S. have received honoraria and travel grants from MSD within the past 3 years. L.I.E. is a scientific adviser to MSD and Abbott Scandinavia AB; his institution has received an institutional grant from MSD. M.E.P. is an employee of MSD. J.M. and G.D.R. have no conflicts of interest
Other bias	Low risk	Appears free of other sources of bias. Study sample size calculation designed to address this review's primary outcome. Treatment groups were mostly comparable in terms of their baseline characteristics and distribution of surgery types

Brueckmann 2015

Methods	**Study design:** randomized, controlled study **Sample size calculation:** powered to detect a significant difference in the incidence of TOFR < 0.9 between groups
Participants	**Number of randomized participants:** 154 **Inclusion criteria:** > 18 years of age, ASA I to III, scheduled to undergo an elective abdominal surgical procedure under general anaesthesia, and expected to undergo neuromuscular relaxation with rocuronium for endotracheal intubation **Exclusion criteria:** suspected difficult intubation; neuromuscular disorder(s); known or suspected severe renal insufficiency (defined as estimated creatinine clearance < 30 mL/min) or significant hepatic dysfunction; history or family history of malignant hyperthermia; allergies to sugammadex, opioids, NMBs, or other medication(s) used during general anaesthesia; toremifene application 24 hours before or within 24 hours after study drug administration; planned ICU admission after surgery or overnight (> 12 hours); stay in the PACU; cardiac pacemaker; pregnancy and breastfeeding; use of any other investigational drugs within 30 days of randomization; or participation in another clinical trial within 30 days
Interventions	**Anaesthesia:** induced and maintained according to clinical need of the participant, and per usual centre practice, with IV induction agents, IV opioids, inhaled anaesthetics, and other agent(s), most commonly a combination of fentanyl, propofol, and sevoflurane **NMBA:** single intubating dose: rocuronium ~ 0.6 mg/kg; maintenance dose: rocuronium ~ 0.15 mg/kg **Comparison:** sugammadex 2 mg/kg or 4 mg/kg (n = 76) vs neostigmine + glycopyrrolate (n = 78) (dosing per usual clinical practice; maximum dose 5 mg) **Administration time of sugammadex or neostigmine:** moderate neuromuscular blockade: TOF 1 to 3 or deep neuromuscular blockade: PTC ≥ 1
Outcomes	**Primary endpoint:** presence of residual neuromuscular blockade at PACU admission, defined as TOFR < 0.9 on arrival to PACU

Brueckmann 2015 *(Continued)*

Key secondary endpoint: time from start of study medication administration to time patient was ready for discharge from the operating room, defined as time point deemed by the providing anaesthesiologist as medically appropriate for the patient to leave the operating room

Exploratory endpoints: Those related to surgical efficiency parameters were also measured

Safety assessments: physical examination at screening and at postanaesthetic visit, vital signs at screening, continuous ECG, oxygen saturation throughout anaesthesia and postoperatively, vital signs at PACU, signs of partial neuromuscular blockade, adverse events and serious adverse events

Notes

Publication type: peer-reviewed article

Country: USA, Massachusetts General Hospital

Conversions: PACU time - range to SD following guidelines from Hozo 2005

Handling of adverse events: More detailed information regarding adverse events possibly, probably, or definitely related to study drug was provided by study authors through email correspondence

Authors' conclusions: After abdominal surgery, sugammadex reversal eliminated residual neuromuscular blockade in the PACU and shortened time from start of study medication administration to time patient was ready for discharge from the operating room

Contact: corresponding trial author M. EIkermann contacted by email: meikermann@partners.org; has replied

* Indicates unpublished data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based randomization*
Allocation concealment (selection bias)	Unclear risk	Sample of 200 sealed envelopes were prepared by the sponsor: 100 for the sugammadex group and 100 for the neostigmine/glycopyrrolate group; however, no information on whether envelopes were sequentially numbered and opaque
Blinding of participants (performance bias)	Low risk	Participants were blinded*
Blinding of personnel (performance bias)	High risk	Anaesthesiologist was unblinded to study drug, as he/she needed to be able to adjust anaesthesia and neuromuscular blockade according to treatment group, and to assess effects of sugammadex on patient flow through the operating room
Blinding of primary outcome assessment (detection bias)	Low risk	TOF-watch assessors were blinded to treatment group, did not observe preparation of trial medications and were not involved in randomization or preparation of study drug, or were not allowed in the operating room during surgery
Blinding of safety assessment (detection bias)	Low risk	Safety assessors were blinded to treatment group, did not observe preparation of trial medications and were not involved in randomization or preparation of study drug, or were not allowed in the operating room during surgery
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants are accounted for, and missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups: 154 participants were randomized (2 were excluded owing to adverse events, 1 withdrew consent), 151 participants received study drug (1 participant was excluded owing to unplanned admission to intensive care

Brueckmann 2015 *(Continued)*

		unit), resulting in 150 participants who had available primary endpoint (sugammadex group n = 74, neostigmine group n = 76)
Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrials.gov (NCT01479764), and all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way
Funding bias	High risk	Declaration of interest: M.K.L. and T.W. are employees of Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA. P.G. is an employee of MSD Oss, The Netherlands. All may own stock and/or hold stock options in the Company. J.de B. was formerly an employee of Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA. M. E., B.B., M.M., J.L., J.K., A.S.S., F.McG., N.S., and R.P. work for institutions that received research funding for conduct of the study from Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA
Other bias	Low risk	Appears free of other sources of bias. Study sample size calculation designed to address this review's secondary outcome. No statistically significant differences regarding baseline characteristics between participant groups

Carron 2013

Methods	**Study design:** randomized clinical trial **Sample size calculation:** based on study's primary and secondary endpoints, powered to detect significant intergroup differences
Participants	**Number of enrolled participants:** 40 female morbidly obese patients **Inclusion criteria:** morbidly obese with BMI ≥ 40 kg/m^2, age ≥18 years, scheduled for laparoscopic removal of adjustable gastric banding under general anaesthesia using rocuronium for tracheal intubation and maintenance of NMB, presence of 1 to 5 post-tetanic counts (PTCs) at completion of surgery **Exclusion criteria:** ASA > III, difficult tracheal intubation, known or suspected disorder affecting NMB, renal and/or hepatic dysfunction, malignant hyperthermia, pregnancy, breastfeeding, and allergy or contraindication to narcotics, NMBAs, sugammadex, neostigmine, or other medications used during anaesthesia
Interventions	**Anaesthesia:** induced with fentanyl 3.5 µg/kg lean body weight (LBW) and propofol 3 mg/kg LBW, maintained with desflurane and remifentanil 0.05 to 0.1 µg/kg/min titrated to a target state entropy value of 35 ± 5 **NMBA:** single intubating dose: rocuronium 0.9 mg/kg ideal body weight (IBW); maintenance dose: rocuronium 0.15 mg/kg **Comparison:** sugammadex 4 mg/kg total body weight (n = 20) vs neostigmine 70 µg/kg LBW + atropine 10 µg/kg (n = 20) **Administration time of sugammadex or neostigmine:** presence of PTC 1 to 5
Outcomes	**Primary endpoint:** difference in anaesthesia time between groups: (1) anaesthesia: time from preoxygenation of participant to tracheal extubation, (2) induction: time from end of preoxygenation to tracheal intubation, (3) maintenance: time from tracheal intubation to beginning of reversal of NMB, (4) reversal: time from reversal of drug administration to TOFR ≥ 0.9, and (5) extubation: time from cessation of desflurane **Secondary endpoints:** differences in oxygen saturation levels and TOFR upon PACU admission and ability to swallow after extubation

Carron 2013 *(Continued)*

	Other considerations: postoperative complications, analgesic and antiemetic requirements, ability to get into bed independently, time to discharge from PACU
Notes	**Publication type:** peer-reviewed article **Country:** Italy **Conversions:** none **Handling of adverse events:** No discrepancy exists between AEs presented in the original article and those reported in this review **Authors' conclusions:** Sugammadex allowed safer and faster recovery from profound rocuronium-induced NMB when compared with neostigmine in participants with MO. Sugammadex may play an important role in fast-track bariatric anaesthesia **Contact:** first trial author Michele Carron contacted by email: micarron@libero.it on 30.09.2015; no reply received. Last author Carlo Ori contacted by email: carloori@unipd.it on 25.10.2015; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated numbers
Allocation concealment (selection bias)	Low risk	"Opening a sealed opaque envelope immediately before surgery by one investigator"
Blinding of participants (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of personnel (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of primary outcome assessment (detection bias)	Unclear risk	No specific information on identity or blinding of TOF-watch assessor
Blinding of safety assessment (detection bias)	Low risk	Safety assessor was not involved in the randomization process and was not present during anaesthesia
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data: 40 patients recruited into the study - 20 allocated to neostigmine group and 20 to sugammadex group
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published article clearly includes all expected outcomes
Funding bias	High risk	Conflict of Interest: Michele Carron has received a payment for lecture from MSD; Mirto Foletto has received a payment for consultancy from Johnson & Johnson Medical; Carlo Ori has received payments and travel funding for lectures and as a member of MSD Advisory Board
Other bias	Low risk	Appears free of other sources of bias. Study sample size calculation designed to address this review's primary outcome. No statistically significant differences in participants' demographic characteristics

Castro 2014

Methods	**Study design:** prospective, controlled, randomized study **Sample size calculation:** no information available
Participants	**Number of randomized participants:** 88 **Inclusion criteria:** morbidly obese (MO) and scheduled for laparoscopic bariatric surgery under general anaesthesia **Exclusion criteria:** lack of consent, followed in chronic pain consultation, already enrolled in another study conducted at our institution (pregabalin effect as preemptive analgesia for surgery in the obese), and previous LBS in the same patient
Interventions	**Anaesthesia:** propofol 1.5 to 2.0 mg/kg CBW, analgesia maintained with remifentanil 0.15 to 0.30 mg/kg CBW, anaesthesia maintained with mixture of oxygen, air, and desflurane in vol % **NMBA:** no information available **Comparison:** sugammadex 2 mg/kg (n = 44) vs neostigmine 0.05 µg/kg + atropine 20 µg/kg (n = 44) **Administration time of sugammadex or neostigmine:** reappearance of T2
Outcomes	Pain using the visual analogue scale at 4 different moments: arrival to PACU, 30 minutes after arrival, 60 minutes after arrival, and immediately before leaving PACU; presence of postoperative nausea and vomits (PONV); and duration of PACU stay before discharge to the ward
Notes	**Publication type:** peer-reviewed article **Country:** Portugal **Conversions:** none **Handling of adverse events:** No discrepancy exists between AEs presented in the original article and those reported in this review **Authors' conclusions:** Sugammadex is associated with less pain in the PACU. This "opioid-sparing" effect, combined with less PONV and faster discharge from the PACU, makes sugammadex an indispensable drug for this type of patient and allows fast-track surgery in the MO **Contact:** first trial author Diogo S. Castro contacted by email: diogosousacastro@hotmail.com on 15.05.2016; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization was performed by the investigator using previously prepared envelopes
Allocation concealment (selection bias)	Unclear risk	Randomization was performed by the investigator using previously prepared envelopes
Blinding of participants (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of personnel (performance bias)	Unclear risk	Unable to assess owing to insufficient information

Castro 2014 *(Continued)*

Blinding of primary outcome assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of safety assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data: 88 eligible participants were randomized into 2 groups of 44; no patients were excluded
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published article clearly includes all expected outcomes
Funding bias	Unclear risk	Unable to assess owing to insufficient information
Other bias	Unclear risk	No apparent other type of bias, except no information on sample size calculation. No differences in participant characteristics between groups

Cheong 2015

Methods	**Study design:** randomized, controlled study **Sample size calculation:** calculated under the presumption that the difference in time to 90% recovery of TOFR between groups was not longer than 30 seconds
Participants	**Number of randomized participants:** 120 **Inclusion criteria:** age between 18 and 65 years, ASA I to II, scheduled for elective surgery **Exclusion criteria:** expected to have difficult intubation owing to anatomical abnormality or limited neck mobility at preoperative evaluation; neuromuscular abnormality; cardiovascular disease; kidney function disorder; liver function disorder; pregnancy; and history of side effects with aesthetics and analgesics. Experiment withdrawal criteria were unexpected massive haemorrhage; unrecovered electrocardiograph (ECG) abnormality; profound hypotension; respiratory abnormality; and TOF device error during experiment
Interventions	**Anaesthesia:** induced with propofol 1.5 to 2.5 mg/kg and maintained with sevoflurane 1.5 to 2.5 vol % and 50% N_2O. **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 5 to 10 mg **Comparison:** sugammadex 2 mg/kg (S2) (n = 30), sugammadex 1 mg/kg (S1) (n = 30), sugammadex 1 mg/kg + neostigmine 0.05 mg/kg + glycopyrrolate 0.01 mg/kg (SN) (n = 30), and neostigmine 0.05 mg/kg + glycopyrrolate 0.01 mg/kg (N) (n = 30) **Administration time of sugammadex, sugammadex + neostigmine, or neostigmine:** reappearance of T1 to 2
Outcomes	Time to 90% recovery of TOFR, adverse events: PONV score, signs of residual blockade, BP, oxygen saturation
Notes	**Publication type:** peer-reviewed article **Country:** Korea **Conversions:** sugammadex time Mean + SD from seconds to minutes

Cheong 2015 *(Continued)*

Handling of adverse events: No discrepancy exists between AEs presented in the original article and those reported in this review

Authors' conclusions: For reversal from rocuronium-induced moderate neuromuscular blockade, combined use of sugammadex and neostigmine may be helpful to decrease recovery time and can reduce the required dosage of sugammadex. However, the increased incidence of systemic muscarinic side effects must be considered

Contact: first trial author Wonjin Lee contacted by email: 2wonjin@hanmail.net on 15.05.2016; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Subjects randomly assigned"; no further information available
Allocation concealment (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of participants (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of personnel (performance bias)	Low risk	To minimize observer bias, drugs were prepared in syringes labelled "reverse" by a third party
Blinding of primary outcome assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of safety assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs: 120 participants were enrolled and randomized, resulting in 4 groups of 30 participants
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published article clearly includes all expected outcomes
Funding bias	Low risk	This work was supported by the 2011 Inje University research grant
Other bias	High risk	Appears free of other sources of bias. Study sample size calculation designed to address this review's primary outcome. Baseline characteristics showed significant differences (P = 0.035) between body weight in 2 groups, which influences the dosage of administered drug and therefore can influence time to recovery of TOFR, MBP, HR, and PONV score

Flockton 2008

Methods	**Study design:** multi-centre, randomized, safety assessor-blinded, parallel-group, phase 3a study (CRYSTAL trial) **Sample size calculation:** powered to detect a difference ≥ 3 minutes in mean time to recovery of TOFR = 0.9 between sugammadex and neostigmine groups

Flockton 2008 *(Continued)*

Participants	**Number of randomized participants:** 84 **Inclusion criteria:** aged ≥ 18 years, ASA class I to III, undergoing surgery in the supine position under general anaesthesia requiring muscle relaxation **Exclusion criteria:** expected to have a difficult intubation for anatomical reasons; neuromuscular disorder or significant renal dysfunction; history or family history of malignant hyperthermia; or known allergy to narcotics, NMBAs, or other medication used during general anaesthesia; receiving antibiotics, anticonvulsants, or magnesium at a time likely to interfere with neuromuscular block; already participated in a previous sugammadex study or any other study within 30 days of entering this study; pregnant, breastfeeding, or of childbearing potential, and not using an adequate method of contraception
Interventions	**Anaesthesia:** induced with IV propofol and remifentanil, fentanyl, or sufentanil; maintained by a continuous infusion of propofol and further increments or infusions of analgesic as needed **NMBA:** single intubating dose: rocuronium 0.6 mg/kg or cisatracurium 0.1 to 0.2 mg/kg; maintenance dose: rocuronium 0.15 to 3 mg/kg or cisatracurium 0.3 mg/kg, up to a maximum of 2 doses **Comparison:** sugammadex 2.0 mg/kg following rocuronium (n = 40) vs neostigmine 50 µg/kg + glycopyrrolate 10 µg/kg following cisatracurium (n = 44) **Administration time of sugammadex or neostigmine:** reappearance of T2
Outcomes	**Primary efficacy variable:** time from start of administration of study drug to recovery of TOFR > 0.9 **Secondary efficacy variables:** time from start of administration of study drug to recovery of TOFR > 0.7 or 0.8 and clinical signs of recovery after extubation, but before transfer to the recovery room and before discharge from the recovery room; time from administration of the intubating dose of rocuronium or cisatracurium to occurrence of maximum block (onset time) **Safety assessments:** adverse events, serious adverse events, monitoring of incidents related to use of the TOF-watch, laboratory variables, physical examination, vital signs
Notes	**Publication type:** peer-reviewed article **Country:** 8 centres in Europe **Conversions:** Median + Range to Mean + SD following guidelines from Hozo 2005 Recovery time to TOFR > 0.9, Mean + SD, from seconds to minutes **Handling of adverse events:** Data presented in Table 3 - "Assessement of clinical signs of recovery" - regarding number of participants with general muscle weakness and number of participants not able to perform 5 second head-lift were considered to be adverse events in this review and were counted as such **Authors' conclusions:** Sugammadex 2 mg/kg administered at reappearance of T2 was significantly faster in reversing rocuronium-induced blockade than neostigmine was in reversing cisatracurium-induced block **Contact:** corresponding trial author Elizabeth Flockton contacted by email: Elizabeth.Flockton@rl-buht.nhs.uk on 10.10.2015; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomization system

Flockton 2008 *(Continued)*

Allocation concealment (selection bias)	Low risk	Central allocation (secondary to central randomization system)
Blinding of participants (performance bias)	Unclear risk	Open-label; no further information available
Blinding of personnel (performance bias)	Unclear risk	Open-label; no further information available
Blinding of primary outcome assessment (detection bias)	Unclear risk	Open-label; no further information available
Blinding of safety assessment (detection bias)	Low risk	Safety assessor was blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants are accounted for, and missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups: 84 participants were randomized to treatment (rocuronium – sugammadex n = 4 0, cisatracurium – neostigmine n = 44), 6 participants did not receive sugammadex (inability to record a stable baseline TOFR in 4 participants, withdrawal of consent in 1, and study medication unavailable in 1), 5 participants did not receive neostigmine (inability to record a stable baseline TOFR in 4 participants, and postponement of surgery in 1), leading to their exclusion from the AST group (n = 73). All treated participants had ≥ 1 efficacy assessment carried out and therefore constituted the ITT population (sugammadex n = 34, neostigmine n = 39)
Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrials.gov (NCT00451100), and all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way
Funding bias	High risk	Declaration of interest: M.E.P. is an employee of N.V. Organon, a part of Schering-Plough Corporation, Oss, The Netherlands. R.K.M. is a member of the Scientific Advisory Board of N.V. Organon, a part of Schering-Plough Corporation
Other bias	Low risk	Appears free of other sources of bias. Study sample size calculation designed to address this review's primary outcome. No clinically relevant differences in baseline characteristics, although the sugammadex group included a higher proportion of women, higher mean age, and a higher percentage of ASA II to III patients compared with the neostigmine group

Foletto 2014

Methods	**Study design:** randomized, controlled trial **Sample-size calculation:** No information available
Participants	**Number of randomized patients:** 34 morbidly obese (MO) patients **Inclusion criteria:** morbidly obese and undergoing laparoscopic-sleeve gastrectomy **Exclusion criteria:** no information available
Interventions	**Anaesthesia:** propofol and remifentanil anaesthesia; no further information available **NMBA:** rocuronium; no further information available

Foletto 2014 *(Continued)*

	Comparison: sugammadex 2 mg/kg (n = 17) vs neostigmine 50 µg/kg (n = 17) **Administration time of sugammadex or neostigmine:** reappearance of T1 to 2
Outcomes	Recovery time to TOFR > 0.9, spirometry 15 minutes postoperative (postoperative forced vital capacity, forced expiratory volume in 1 second, peak expiratory flow)
Notes	**Publication type:** meeting abstract **Country:** Italy **Conversions:** none **Authors' conclusions:** Respiratory function was restored more quickly in morbidly obese participants who received sugammadex to reverse rocuronium-induced NMB **Contact:** first trial author Mirto Foletto contacted by email: mirto.foletto@unipd.it on 07.10.2015; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Random"; no further information
Allocation concealment (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of participants (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of personnel (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of primary outcome assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of safety assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to assess owing to insufficient information
Selective reporting (reporting bias)	Unclear risk	Unable to assess owing to insufficient information
Funding bias	Unclear risk	Unable to assess owing to insufficient information
Other bias	Unclear risk	No differences in participant characteristics, anaesthetic drugs, and baseline spirometry were observed between groups. No information on sample size calculation was provided

Gaszynski 2011

Methods	**Study design:** prospective, randomized study **Sample size calculation:** no information available
Participants	**Number of randomized participants:** 70 **Inclusion criteria:** morbidly obese (BMI > 40 kg/m^2) and undergoing elective bariatric surgery **Exclusion criteria:** lack of consent, coexisting muscular disease, severe cardiovascular disease (NYHA > II)
Interventions	**Anaesthesia:** Induction with propofol 1.5 to 2 mg/kg CBW (corrected body weight), fentanyl 0.05 mg/kg CBW for intraoperative analgesia. Maintainance with desflurane **NMBA:** single intubating dose: rocuronium 1 mg/kg CBW; maintenance dose: rocuronium 0.06 mg/kg CBW, maximum 2 additional doses **Comparison:** sugammadex 2 mg/kg CBW (n = 35) vs neostigmine 50 µg/kg CBW + atropine 20 µg/kg CBW (n = 35) **Administration time of sugammadex or neostigmine:** reappearance of T2
Outcomes	Neuromuscular function was recorded and time to achieve 90% of TOF (safe extubation) was measured. PORC (postoperative residual curarization) was measured using TOF stimulation. Neuromuscular monitoring in the PACU
Notes	**Publication type:** peer-reviewed article **Country:** Poland **Conversions:** recovery time to TOFR > 0.9, Mean + SD, from seconds to minutes **Handling of adverse events:** No discrepancy exists between AEs presented in the original article and those reported in this review **Authors' conclusions:** Administration of sugammadex provides fast recovery of neuromuscular function and prevents postoperative residual curarization (PORC) in the morbidly obese; however, neostigmine does not **Contact:** first trial author T. Gaszynski contacted by email: tomgaszyn@poczta.onet.pl on 07.10.2015; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Previously prepared envelopes"; no further information
Allocation concealment (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of participants (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of personnel (performance bias)	Unclear risk	Unable to assess owing to insufficient information

Gaszynski 2011 *(Continued)*

Blinding of primary outcome assessment (detection bias)	Unclear risk	No specific information on identity or blinding of TOF-watch assessor. Study investigator measuring PORC using TOF stimulation was blinded
Blinding of safety assessment (detection bias)	Unclear risk	No specific information on identity or blinding of safety assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	70 participants were enrolled and randomized - 35 in each group. All participants are accounted for, and no outcome data are missing
Selective reporting (reporting bias)	Unclear risk	Study was registered with SYNABA - The Polish Clinical Trials Authorization, ref nr. 252922. Study's primary and secondary outcomes/efficacy endpoints are not clearly stated in the published paper
Funding bias	Unclear risk	T.G. is a member of the national advisory committee on introduction of sugammadex into clinical practice. T.G. has received an honorarium from MSD Company for lectures during scientific meetings on use of neuromuscular blocking agents in general anaesthesia. Study was sponsored by government grant no. N N403 3755 33
Other bias	Unclear risk	No apparent other type of bias, except no information on sample size calculation. No difference in participant characteristic data and total dose of rocuronium between groups

Geldner 2012

Methods	**Study design:** randomized, active-controlled, parallel-group, multi-centre, safety assessor-blinded trial **Sample size calculation:** powered to detect a difference with respect to length of stay in theatre and post-anaesthesia recovery unit between the 2 treatments of half a standard deviation
Participants	**Number of randomized participants:** 140 **Inclusion criteria:** age ≥ 18 years; ASA physical status I to III; scheduled laparoscopic cholecystectomy or appendectomy under general anaesthesia; and written, informed consent **Exclusion criteria:** suspected difficult tracheal intubation; disorder affecting neuromuscular blockade; known or suspected significant renal dysfunction; known or suspected severe hepatic dysfunction; history of malignant hyperthermia; allergy to opioids, neuromuscular blocking drugs, or other medications used during general anaesthesia; contraindication to neostigmine and/or atropine; pregnancy (excluded both by medical history and by a human chorionic gonadotropin test within 24 hours of surgery in women of childbearing age) and breastfeeding; already participated in another sugammadex study or participated in another clinical study not preapproved by the sponsor within 30 days
Interventions	**Anaesthesia:** induced and maintained using intravenous propofol and opioids (most frequently fentanyl) as required; choice and dose of which were decided by the responsible anaesthetist **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 0.1 to 0.2 mg/kg **Comparison:** sugammadex 4 mg/kg (n = 70) vs neostigmine 50 µg/kg + atropine 10 µg/kg (n = 70) **Administration time of sugammadex or neostigmine:** PTC 1 to 2 for sugammadex and reappearance of T2 for neostigmine + atropine
Outcomes	**Primary efficacy parameter:** time from start of sugammadex or neostigmine administration to TOFR > 0.9

Geldner 2012 *(Continued)*

	Secondary outcome parameters: safety and length of stay in the operating room and the PACU following administration of study drug **Safety assessments:** adverse events, vital signs, physical examination findings
Notes	**Publication type:** peer-reviewed article **Country:** European study - 3 centres in Russia, 4 in Germany, 2 in Finland, and 1 in UK **Conversions:** none **Handling of adverse events:** No discrepancy exists between AEs presented in the original article and those reported in this review **Authors' conclusions:** In participants undergoing laparoscopic surgery under propofol anaesthesia, neuromuscular blockade reversal with sugammadex administered at a PTC of 1 to 2 (deep neuromuscular blockade) after rocuronium was well tolerated and resulted in faster recovery of the TOFR to 0.9 compared with neostigmine administered at reappearance of T2 (moderate neuromuscular blockade) (P < 0.0001). Sugammadex therefore may allow rapid reversal of deep neuromuscular blockade at completion of surgery without a delay in recovery **Contact:** first trial author G. Geldner contacted by email: goetz.geldner@kliniken-lb.de; has replied

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Online randomization list created by Orcapharma (Heesch, The Netherlands) using the software package SAS̀ (SAS Institute, Cary, NC, USA) in compliance with international protocols
Allocation concealment (selection bias)	Low risk	Central allocation (secondary to web randomization)
Blinding of participants (performance bias)	Low risk	Participants were blinded
Blinding of personnel (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of primary outcome assessment (detection bias)	Unclear risk	No specific information on identity or blinding of the TOF-watch assessor
Blinding of safety assessment (detection bias)	Low risk	Safety assessor was blinded to treatment assignment, was not involved in the randomization process, was not present during anaesthesia, and was not involved in preparation of the trial medication
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants are accounted for, and missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups: 140 participants were assigned to sugammadex (70) or neostigmine (70); 4 participants in the sugammadex group and three in the neostigmine group did not receive study drug. Two participants in the neostigmine group were not included in the efficacy analysis because of failure of the neuromuscular monitoring device. Data were imputed by a conservative approach towards sugammadex for 3 participants in the sugammadex group and 5 in the neostigmine group, because time to recovery of the TOFR to 0.9 was not available. Out of these, for 2 in the sugammadex group and 2 in the neostigmine group, the TOFR did not reach 0.9; for the remaining 2 participants, times were consid-

Geldner 2012 *(Continued)*

		ered unreliable owing to an unstable trace (neostigmine group) or unsuccessful calibration (sugammadex group)
Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrials.gov (NCT00724932), and all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way
Funding bias	High risk	Study sponsor, MSD, was involved in both study design and analysis of the data. The overall design and conduct of the study, as well as final analysis of study data and opinions, conclusions, and interpretation of the data, are the responsibility of the study authors. Medical writing assistance was provided by Neil Venn, PhD, of Prime Medica Ltd (Knutsford, UK); this assistance was funded by Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ. The study sponsor was allowed to review the manuscript before submission, but final decisions on content remained the responsibility of trial authors, and all trial authors approved the final text of the manuscript before submission Götz Geldner has acted as a scientific advisor to MSD (formerly Organon) and GlaxoSmithKline and has delivered lectures for and received research funding from both companies. Henk Rietbergen is an employee of MSD. The other study authors declare no competing interests
Other bias	High risk	

Georgiou 2013

Methods	**Study design:** randomized controlled trial **Sample size calculation:** no information available
Participants	**Number of randomized participants:** 57 **Inclusion criteria:** super-obese (SO) (BMI > 50 kg/m^2) scheduled for open bariatric surgery **Exclusion criteria:** cardiovascular disease (NYHA > 2); refusal to participate in the study; contraindication to epidural catheter placement (e.g. anticoagulation, anti-platelet medication); coexisting neuromuscular disease; history of allergic reaction to neuromuscular blocking agents; history of difficult intubation; creatinine levels > 159 mmol/L
Interventions	**Anaesthesia:** propofol and remifentanil **NMBA:** single intubating dose: rocuronium, dose not available; maintenance dose: not specified **Comparison:** sugammadex 2 mg/kg ideal body weight (n = 15) vs sugammadex 2 mg/kg corrected body weight (n = 13) vs neostigmine 50 µg/kg ideal body weight (n = 14) vs neostigmine 50 µg/kg corrected body weight (n = 15) **Administration time of sugammadex or neostigmine or placebo:** reappearance of T2
Outcomes	**Primary endpoint:** full decurarization **Secondary endpoint:** ability to get into bed independently on arrival to the PACU and clinical signs of residual paralysis
Notes	**Publication type:** meeting abstract **Country:** Greece

Georgiou 2013 *(Continued)*

Conversions: recovery time to TOFR > 0.9, Mean + SD, from seconds to minutes

Authors' conclusions: Although transfer times to wards in neostigmine groups were ˜ 53 minutes longer than those in sugammadex groups, the cost of Sugammadex was > 400 times higher than the cost of neostigmine. Under current economic crisis conditions, one should take this seriously into consideration

Contact: first trial author P. Georgiou contacted by email: prgeorg@yahoo.gr: 09.10.2015; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned"; no further information
Allocation concealment (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of participants (performance bias)	Low risk	Participants blinded
Blinding of personnel (performance bias)	Unclear risk	Investigator blinded; no further information available
Blinding of primary outcome assessment (detection bias)	Unclear risk	Investigator blinded; no further information available
Blinding of safety assessment (detection bias)	Unclear risk	Investigator blinded; no further information available
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrials.gov (NCT01629394), and all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way
Funding bias	Low risk	University of Patras
Other bias	Unclear risk	Unable to assess owing to insufficient information

Grintescu 2009

Methods	**Study design:** open randomized trial **Sample size calculation:** no information available
Participants	**Number of randomized participants:** 34 **Inclusion criteria:** undergoing laparoscopic cholecystectomy **Exclusion criteria:** no information available

Grintescu 2009 *(Continued)*

Interventions	**Anaesthesia:** propofol, remifentanil, and sevoflurane **NMBA:** rocuronium; no further information available **Comparison:** sugammadex 2 mg/kg (n = 17) vs neostigmine 50 µg/kg (n = 17) **Administration time of sugammadex or neostigmine:** moderate residual block
Outcomes	Total time spent by participant in the operating theatre complex, surgical procedure time, and time between reversal agent administration and extubation (recovery time)
Notes	**Publication type:** meeting abstract **Country:** Romania **Conversions:** none **Authors' conclusions:** Sugammadex reduces total time spent in the operating theatre by providing fast and reliable recovery from neuromuscular block with no risk of postoperative residual curarization. In daily practice, this could improve the use of operating theatre facilities and could lower the total cost of a surgical procedure **Contact:** first trial author Ioana Grintescu contacted by email: ioana.grintescu@rospen.ro on 11.10.2015; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Allocation concealment (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of participants (performance bias)	High risk	Open randomized trial; no further information available
Blinding of personnel (performance bias)	High risk	Open randomized trial; no further information available
Blinding of primary outcome assessment (detection bias)	High risk	Open randomized trial, no further information available
Blinding of safety assessment (detection bias)	High risk	Open randomized trial; no further information available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to assess owing to insufficient information
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published meeting abstract clearly includes all expected outcomes
Funding bias	Unclear risk	Unable to assess owing to insufficient information
Other bias	Unclear risk	Unable to assess owing to insufficient information

Hakimoglu 2016

Methods	**Study design:** randomized, controlled trial **Sample size calculation:** powered to detect a 15% change in IOP (intraocular pressure) between groups
Participants	**Number of randomized participants:** 60 **Inclusion criteria:** age 18 to 65 years, ASA I to II, undergoing arthroscopic surgery under general anaesthesia **Exclusion criteria:** chronic diseases other than hypertension; previous ocular disease or ocular surgery, allergy to tetracaine or other agents used in anaesthesia
Interventions	**Anaesthesia:** induced using propofol 2.5 mg/kg and fentanyl 1.0 µg/kg, maintained using desflurane 4% to 6% (3 L/min) in a 50:50% oxygen/air mixture **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: no information available **Comparison:** sugammadex 4 mg/kg (n = 30) vs neostigmine 0.05 mg/kg + atropine 0.015 mg/kg (n = 30) **Administration time of sugammadex or neostigmine:** reappearance of T2
Outcomes	**Primary outcome:** evaluation of intraocular pressure changes with sugammadex and neostigmine + atropine with a Tono-Pen XL applanation tonometer, measured before induction and at 30 seconds and 2 and 10 minutes after extubation **Secondary outcomes:** investigation of the effects of sugammadex and neostigmine on haemodynamic parameters (heart rate, mean arterial pressure, peripheral arterial oxygen saturation), measured by electrocardiography, non-invasive oscillometry method, and pulse oximetry. Also investigation of effects of sugammadex and neostigmine on complications (gagging, nausea, vomiting, breath holding, laryngospasm, and tremors) after extubation
Notes	**Publication type:** peer-reviewed article **Country:** Turkey **Conversions:** none **Handling of adverse events:** No discrepancy exists between AEs presented in the original article and those reported in this review **Authors' conclusions:** Postextubation IOP values for the sugammadex group were similar to those for the neostigmine-atropine group. Additionally, in agreement with previous studies, extubation time in our study was found to be shorter in the sugammadex group than in the neostigmine-atropine group. Additional studies that include more participants are needed **Contact:** first trial author Sedat Hakimoglu contacted by email: sedathakimoglu@gmail.com on 15.05.2016; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomized by "computer-generated random numbers"
Allocation concealment (selection bias)	Unclear risk	Unable to assess owing to insufficient information

Hakimoglu 2016 *(Continued)*

Blinding of participants (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of personnel (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of primary outcome assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of safety assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs: 60 patients were enrolled and randomized, resulting in 30 participants in each group
Selective reporting (reporting bias)	Low risk	Study protocol was retrospectively registered on ANZCTR - Australian New Zealand Clinical Trials Registry (ACTRN12614000651684), and all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way
Funding bias	Unclear risk	All trial authors declare no conflicts of interest; no information on funding provided
Other bias	Low risk	Study sample size calculation designed to address this review's secondary outcome. No significant differences detected between groups when demographic data and anaesthesia time were compared

Illman 2011

Methods	**Study design:** double-blinded, randomized, multi-centre study **Sample size calculation:** powered to detect a 7-minute difference in time from administration of neostigmine or sugammadex to achievement of TOFR of 0.9
Participants	**Number of randomized participants:** 50 **Inclusion criteria:** both genders, age 18 to 70, BMI < 32.5, scheduled for elective surgery requiring general anaesthesia **Exclusion criteria:** clinically significant renal, hepatic, or ventilatory dysfunction; increased intracranial pressure; pregnancy or lactation; muscular dystrophies, myopathy, or cerebral palsy; history of intolerance to any of the study drugs; taking medication known to interfere with neuromuscular transmission; simultaneous participation in other studies
Interventions	**Anaesthesia:** induced by propofol and an opioid, according to routine of the study centre, maintained by a volatile anaesthetic (sevoflurane or desflurane), together with opioids **NMBA:** single intubating dose: rocuronium 0.6 to 1 mg/kg; maintenance dose: rocuronium 5 to 10 mg **Comparison:** sugammadex 2 mg/kg (n = 25) vs neostigmine 50 µg/kg + glycopyrrolate 10 µg/kg (n = 25) **Administration time of sugammadex or neostigmine:** reappearance of T1 to 2
Outcomes	**Main objective:** time gap between loss of visual fade to return of TOFR = 0.9, i.e. potentially unsafe period of recovery

Illman 2011 *(Continued)*

	Secondary endpoints: times for return of TOFR to 0.70, 0.80, 0.90 after reversal; TOFR at loss of visual fade; time of tracheal extubation **Safety assessment:** any adverse events, time, severity, and duration
Notes	**Publication type:** peer-reviewed article **Country:** Finland, 2 centres **Conversions:** none **Handling of adverse events:** No discrepancy exists between AE presented in the original article and those reported in this review **Authors' conclusions:** A significant time gap occurs between visual loss of fade and return of TOFR > 0.9 after reversal of a rocuronium block by neostigmine. Sugammadex in comparison with neostigmine allows safer reversal of a moderate NMB when relying on visual evaluation of the TOF response **Contact:** first trial author Hanna Illman contacted by email: hanna.illman@tyks.fi on 12.10.2015; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes containing written instructions to prepare neostigmine or sugammadex, no specific information on whether envelopes were opaque and sequentially numbered
Blinding of participants (performance bias)	Low risk	Participants were blinded to treatment groups as randomization occurred while participants were under general anaesthesia
Blinding of personnel (performance bias)	Low risk	Anaesthesiologist was blinded to reversal drug throughout anaesthesia
Blinding of primary outcome assessment (detection bias)	Low risk	Anaesthesiologist, who also was the TOF-watch assessor, was blinded
Blinding of safety assessment (detection bias)	Unclear risk	No specific information on identity or blinding of safety assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants are accounted for, and missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups: All enrolled participants completed the study, but 2 participants from the neostigmine group and 1 from the sugammadex group were excluded. Reasons for exclusion included technical failure of TOF-watch in 2 participants (1 each from the neostigmine and sugammadex groups), and 1 participant (from the neostigmine group) awoke from anaesthesia before TOFR = 0.90 was established. Accordingly, 23 participants in the neostigmine group and 24 in the sugammadex group were included in the analysis
Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrialsregister.eu (Eudra CT 2009-013537-22), and all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way

Illman 2011 *(Continued)*

Funding bias	High risk	Study was supported by Finnish MSD (Finnish Schering-Plough, Inc.). Disclosure: Klaus T. Olkkola, Olli A. Meretoja, and Seppo Alahuhta are members of the advisory board of Finnish MSD and have received lecture honoraria from Finnish MSD. Hanna Illman has received lecture honoraria from Finnish MSD and MSD Inc. (Schering-Plough Inc.)
Other bias	Low risk	Appears free of other sources of bias. Study sample size calculation designed to address this review's primary outcome. No significant differences between patient groups and in conduct of anaesthesia

Isik 2016

Methods	**Study design:** randomized, controlled study **Sample size calculation:** powered to detect a minimum difference of 10% in values of Cystatin C between the 2 groups
Participants	**Number of randomized participants:** 50 **Inclusion criteria:** between the ages of 18 and 65 years, ASA I to II, scheduled for elective surgery under general anaesthesia with normal renal function (serum Cr < 1.5 mg/dL) **Exclusion criteria:** liver failure, kidney failure, neuromuscular disorders, pregnant or breastfeeding, treated with corticosteroids or oral contraceptives, contraindication to study drugs, allergy to study drugs, BMI > 30 kg/m^2, receiving medication known to interfere with the action of rocuronium (e.g. amino glycoside antibiotics and anticonvulsants), or did not wish to participate
Interventions	**Anaesthesia:** induced with fentanyl 2 µg/kg and propofol 2 mg/kg, Maintainance: 60% N_2O-O_2 and 4% to 6% desflurane **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 0.15 mg/kg **Comparison:** sugammadex 4 mg /kg at reappearance of PTC 1 to 2 or T2 (n = 25) vs neostigmine 40 µg/kg + 10 at reappearance of T2 (n = 25) **Administration time of sugammadex or neostigmine:** reappearance of PTC 1 to 2 or T2
Outcomes	**Primary endpoint:** acute effects of sugammadex or neostigmine on renal function Serum Cys C, Cr urea, blood urea nitrogen (BUN), sodium (Na), potassium (K), and calcium (Ca) levels and urine a1µg, b2µg, and µA levels were preoperatively and postoperatively determined
Notes	**Publication type:** peer-reviewed article **Country:** Turkey **Conversions:** none **Authors' conclusions:** We believe that the use of more specific and sensitive new-generation markers like cystatin C to evaluate kidney function will result in better understanding and interpretation of our results. Sugammadex has more tolerable effects on kidney function than does neostigmine. However, comparison with preoperative values yields a negative alteration of postoperative values. Neostigmine and sugammadex do not cause renal failure but may affect kidney function **Contact:** first trial author Isik Yasemin contacted by email: yaseminmd@yahoo.com on 24.05.2016; no reply received

Risk of bias

Isik 2016 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization sequence was generated by using computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Randomziation was performed by one of the review authors, who used previously prepared, sealed, opaque envelopes
Blinding of participants (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of personnel (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of primary outcome assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of safety assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published article clearly includes all expected outcomes
Funding bias	Low risk	Study supported by Yuzuncu Yil University, Department of Scientific Research Projects; study authors have no conflicts of interest
Other bias	Low risk	Study sample size calculation designed to address this review's secondary outcome. Baseline characteristics data and total rocuronium doses were comparable in both groups

Jones 2008

Methods	**Study design:** phase 3, multi-centre, randomized, parallel-group, safety assessor-blinded study (SIGNAL study) **Sample size calculation:** powered to detect a difference of 5 minutes or greater from start of administration of Org 25969/neostigmine to recovery T4/T1 ratio to 0.9 between treatment groups
Participants	**Number of randomized participants:** 88 **Inclusion criteria:** ASA I to IV, > 18 years, scheduled to undergo elective surgery during general anaesthesia in supine position. **Exclusion criteria:** expected difficult airway; known or suspected neuromuscular disorders that might impair neuromuscular blockade; significant renal dysfunction; a (family) history of malignant hyperthermia; allergy to narcotics, muscle relaxants, or other medications used during anaesthesia; receiving medication at a dose and/or time known to interfere with NMBAs (e.g. antibiotics, anticonvulsants, magnesium salts); use of neostigmine and/or glycopyrrolate was contraindicated; female patients who were pregnant, breastfeeding, or of childbearing age and were not using reliable birth control; already participated in another clinical trial within 30 days of entering this study

Jones 2008 *(Continued)*

Interventions	**Anaesthesia;** induced with IV opioid and propofol, maintained with intravenous opioid and sevoflurane **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 0.15 mg/kg **Comparison:** sugammadex 4.0 mg/kg (n = 48) vs neostigmine 70 µg/kg + 14 µg/kg glycopyrrolate (n = 40) **Administration time of sugammadex or neostigmine:** reappearance of PTC 1 to 2
Outcomes	**Primary efficacy parameter:** time from start of administration of Org 25969/neostigmine to recovery T4/T1 ratio to 0.9 **Secondary efficacy variables:** time from start of administration of Org 25969/neostigmine to recovery T4/T1 ratio to 0.7 and 0.8; assessment of clinical signs of recovery (level of consciousness, 5 second head-lift, general muscle weakness) **Safety assessment:** adverse events, serious adverse events, physical examination, vital signs, blood samples, urine samples
Notes	**Publication type:** peer-reviewed article **Country:** USA, 9 centres **Conversion:** Median + Range to Mean + SD following guidelines from Hozo 2005 **Handling of adverse events:** Data presented in the "Efficacy results" section (page 821, paragraph 2) regarding number of participants with general muscle weakness and number not able to perform 5 second head-lift were considered to show adverse events in this review and were counted as such **Authors' conclusions:** Recovery from profound rocuronium-induced neuromuscular blockade was significantly faster with sugammadex than with neostigmine, suggesting that sugammadex has a unique ability to rapidly reverse profound rocuronium neuromuscular blockade **Contact:** first trial author R. Kevin Jones contacted by email: kevinjones@accurateclinicaltrials.net on 23.09.2015; no reply received * Indicates unpublished data collected by authors of the previous review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated" * Participants were randomly assigned to treatment groups according to a randomization schedule card prepared in advance by Schering-Plough
Allocation concealment (selection bias)	Low risk	Randomization lists were kept by the person who was responsible for preparing the medication (or placebo). This person was not involved in administering the medication to participants, nor in participants' care or data collection *
Blinding of participants (performance bias)	High risk	Open-label study; no further information available
Blinding of personnel (performance bias)	High risk	Open-label study; no further information available
Blinding of primary outcome assessment (detection bias)	Unclear risk	No specific information on identity or blinding of TOF-watch assessor

Jones 2008 *(Continued)*

Blinding of safety assessment (detection bias)	Low risk	Blinded safety assessor (who was not involved in randomization of participants nor in preparation or administration of trial medication or allowed in the operating room during surgery) performed a physical examination before surgery and during the postanaesthetic visit, as well as monitored all participants for adverse and serious adverse events
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants are accounted for in the article, and missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups: 88 participants were randomized in the rocuronium arm of the study - 48 to sugammadex and 40 to neostigmine. 14 (sugammadex n = 11, neostigmine n = 3) discontinued the study. 13 of these discontinued before receiving rocuronium or study drug, primarily for surgery-related reasons; 1 participant in the sugammadex group discontinued after receiving rocuronium prematurely. Therefore, the all-subjects-treated group comprised 75 participants (sugammadex n = 37, neostigmine n = 38), and the intent-to-treat group comprised 74 participants (n = 37 in each group)
Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrials.gov (NCT00473694), and all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way
Funding bias	High risk	Supported by Schering-Plough, Roseland, New Jersey
Other bias	Low risk	Appears free of other sources of bias. Study sample size calculation designed to address this review's primary outcome. Treatment groups generally comparable with respect to baseline characteristics

Kaufhold 2016

Methods	**Study design:** Single-centre, randomized, parallel-group, double-blinded study (SUNDRO20) **Sample size calculation:** powered to detect doses necessary to accelerate time between study drug administration at a TOFR ≥ 0.2 to a TOFR ≥ 0.9 in 50% of participants within 2 minutes
Participants	**Number of randomized participants:** 99 **Inclusion criteria:** age > 18 years; ASA physical status I to III; undergoing elective surgery under general anaesthesia with rocuronium for tracheal intubation; written informed consent **Exclusion criteria:** expected to have a difficult airway or with known neuromuscular disease, significant hepatic or renal dysfunction, family history of malignant hyperthermia, known allergy to one of the drugs used in this protocol; or intake of any medication that might interact with muscle relaxants; pregnant women or women who were breastfeeding; individuals who have participated in another clinical study in the past 30 days
Interventions	**Anaesthesia:** induced with propofol 2 to 3 mg/kg IV and fentanyl 0.1 to 0.2 µg/kg IV and maintained with propofol and remifentanil according to clinical need and preference for the anaesthetist **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 0.1 to 0.2 mg/kg **Comparison:** sugammadex 0.25 mg/kg (n = 9), 0.5 mg/kg (n = 9), 0.75 mg/kg (n = 9), 1.0 mg/kg (n = 9), and 1.25 mg/kg (n = 9), neostigmine 10 µg/kg (n = 9), 25 µg/kg (n = 9), 40 µg/kg (n = 9), 55 µg/kg (n = 9), and 70 µg/kg (n = 9) in a mixture with 1 µg glycopyrrolate per 5 µg neostigmine, or saline (n = 9) **Administration time of sugammadex or neostigmine or placebo:** TOFR ≥ 0.2

Kaufhold 2016 *(Continued)*

Outcomes	**Primary endpoints:** doses necessary to achieve this effect in 50% of patients within 2 minutes or in 95% of patients within 5 minutes **Secondary endpoints:** doses for less advanced acceleration (i.e. in 50% of participants within 5 minutes or in 95% of participants within 10 minutes) **Safety assessment:** heart rate, blood pressure, and clinical muscle test function (eye opening, head-lift test, arm-lift test, swallowing a bolus of 20 mL of water, test for general muscle weakness)
Notes	**Publication type:** peer-reviewed article **Country:** Germany **Conversions:** none **Handling of adverse events:** No discrepancy exists between AEs presented in the original article and those reported in this review **Authors' conclusions:** A residual neuromuscular block for a TOFR = 0.2 cannot be reversed reliably with neostigmine within 10 minutes. In the conditions studied, substantially lower doses of sugammadex than the approved dose of 2.0 mg/kg may be sufficient to reverse residual rocuronium-induced neuromuscular block at recovery of TOFR ≥ 0.2 **Contact:** first trial author S. Schaller contacted by email: s.schaller@tum.de on 07.06.2016; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomization list"; every participants received a consecutive number
Allocation concealment (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of participants (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of personnel (performance bias)	Low risk	In the operating room, unblinded study staff attending anaesthetist, who was the only person with access to the randomization list, prepared the study drug corresponding to the randomization number in an unlabelled syringe. Upon request of the blinded anaesthetist, responsible for the participant (without access to the randomization list and study medication); unlabelled study drug was injected
Blinding of primary outcome assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of safety assessment (detection bias)	Low risk	Safety assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants are accounted for, and missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups: A total of 99 participants were initially enrolled after 109 had been screened. One participant, who had received neostigmine 70 µg/kg, withdrew his written informed consent after surgery. Therefore, 98 participants were included in statistical analysis. No protocol violations occurred

Kaufhold 2016 *(Continued)*

Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrials.gov (NCT01006720), and all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way
Funding bias	High risk	Declaration of interest: N.K. has received a travel grant from MSD Sharpe & Dohme. S.J.S. holds stocks for the following companies in the healthcare sector in small amounts: Bayer AG, Siemens AG, GE, Merck & Co. Inc., Rhoen-Klinikum AG, and Fresenius SE; however, these holdings did not influence any decisions regarding the study. C.G.S. has received honoraria and a travel grant from MSD Sharpe & Dohme. H.F. has received honoraria and travel grants from the following companies: MSD Sharp & Dohme, Essex, Baxter, Care Fusion, and GE Healthcare. M.B. has received honoraria and travel grants from MSD Sharp & Dohme and GlaxoSmithKline. E.B. and K.U. have declared no conflicts Funding: Klinik für Anaesthesiologie, Klinikum rechts der Isar der Technischen Universität München, Munich, Germany
Other bias	High risk	Study sample size calculation not designed to address this review's primary or secondary outcome. Groups did not differ regarding age, weight, height, sex, and ASA physical status

Khuenl-Brady 2010

Methods	**Study design:** multi-centre, randomized, active control, safety assessor-blinded trial **Sample size calculation:** no information available
Participants	**Number of randomized participants:** 100 **Inclusion criteria:** age ≥ 18 years, ASA I to III, scheduled for a surgical procedure under general anaesthesia in a supine position requiring tracheal intubation **Exclusion criteria:** anticipated difficult airway; known or suspected neuromuscular disorders; significant renal dysfunction; known or suspected family history of malignant hyperthermia; allergy to narcotics, muscle relaxants, or other medication used during general anaesthesia; receiving medication at a dose and/or time point likely to interfere with NMBDs and for whom use of neostigmine and/or glycopyrrolate could be contraindicated; participated in a previous sugammadex trial, pregnant, breastfeeding, or female of childbearing age using only hormonal contraception or no means of birth control
Interventions	**Anaesthesia:** induced with IV opioid (at the discretion of the investigator) and IV propofol, maintained with sevoflurane MAC 1 to 2 and opioids, according to each participant's needs **NMBA:** single intubating dose: vecuronium 0.1 mg/kg; maintenance dose: vecuronium 0.02 to 0.03 mg/kg **Comparison:** sugammadex 2 mg/kg (n = 51) vs neostigmine 50 µg/kg + glycopyrrolate 10 µg/kg (n = 49) **Administration time of sugammadex or neostigmine:** reappearance of T2
Outcomes	**Primary efficacy variable:** time from start of administration of sugammadex or neostigmine to recovery of TOFR to 0.9 **Secondary efficacy variables:** time from start of administration of sugammadex or neostigmine to recovery of TOFR to 0.7, time to recovery of TOFR to 0.8, and assessments of clinical signs of recovery (level of consciousness, 5 second head-lift test, and general muscle weakness) before transfer to the recovery room after tracheal extubation and before discharge from the recovery room

Khuenl-Brady 2010 *(Continued)*

	Safety assessments: pretreatment events; serious trial procedure-related events (up to 7 days post dose); vital signs, blood samples, urinalysis, adverse events, and serious adverse events; physical examination findings; clinical signs of possible residual paralysis or recurrence of neuromuscular block
Notes	**Publication type:** peer-reviewed article **Country:** 13 centres in Europe: Austria, Belgium, Germany, Italy, Spain, Sweden, and United Kingdom **Conversions:** Median + Range to Mean + SD following guidelines from Hozo 2005 **Handling of adverse events:** Data presented in the "Efficacy results" section (last paragraph on page 68 and first paragraph on page 69) regarding number of participants with general muscle weakness and not able to perform 5 second head-lift, which were considered adverse events in this review and were counted as such **Authors' conclusions:** Sugammadex provided significantly faster reversal of vecuronium-induced neuromuscular blockade compared with neostigmine **Contact:** first trial author Karin S. Khuenl-Brady contacted by email: karin.khuenl-brady@i-med.ac.at on 15.10.2010; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomization system, part of a secure trial website
Allocation concealment (selection bias)	Low risk	All enrolled participants were allocated a subject number in sequential order of their enrolment into the trial and received a treatment code using the central randomization system
Blinding of participants (performance bias)	High risk	Open-label; no further information available
Blinding of personnel (performance bias)	High risk	Open-label; no further information available
Blinding of primary outcome assessment (detection bias)	High risk	Open-label; no further information available
Blinding of safety assessment (detection bias)	Low risk	Safety assessor was blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	All participants are accounted for, but missing outcome data are not balanced in numbers across intervention groups, as 25% fewer participants are included in the neostigmine group compared with the sugammadex group: 100 participants were enrolled in the study: 51 randomized to the sugammadex group and 49 to the neostigmine group. Three participants in the sugammadex group and 4 in the neostigmine group did not receive study drug. Reasons for discontinuation in the sugammadex group were refusal of surgical procedure (n = 1) and TOF-watch SX problems (n = 2). In the neostigmine group, participants were discontinued because of unavailability of site staff to perform the protocol (n = 1), randomization failure (n = 1), surgeon's withdrawal of consent for operating room time for the research team (n = 1), and a TOF-watch SX problem (n = 1). Hence, 48 participants in the sugammadex group and 45 in the neostigmine group were treated (representing the all-subjects-treated population). Data were excluded for 2 participants in the sugam-

Khuenl-Brady 2010 *(Continued)*

		madex group as TOF data to 0.9, 0.8, and 0.7 were considered unreliable because of unstable TOF baseline Data were excluded for 11 participants in the neostigmine group because TOF data to 0.9 were missing (8 participants failed to achieve a TOFR of 0.9; 1 participant did not have recovery time measured for TOFR 0.9, and in 2 participants, TOFR data to 0.9 were considered unreliable because of unstable TOFR baseline)
Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrials.gov (NCT00451217), and all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way
Funding bias	High risk	Supported by Schering-Plough, Oss, The Netherlands. Henk Rietbergen is employed by Schering-Plough
Other bias	Unclear risk	No apparent other type of bias, except no information on sample size calculation. Treatment groups had similar baseline characteristics

Kizilay 2016

Methods	**Study design:** prospective, randomized study **Sample size calculation:** no information available
Participants	**Number of randomized participants:** 90 **Inclusion criteria:** aged 18 to 75 with grade 2 or 3 cardiovascular disease according to New York Heart Association classification undergoing non-cardiac surgery; free of any clinical infection; chronic alcohol use or substance abuse history; free of contraindications to atropine, neostigmine, or sugammadex **Exclusion criteria:** did not give written consent;respiratory or cardiac arrest, cerebral bleeding, ischaemia, infarct, or hypersensitivity reaction to any of the study medications
Interventions	**Anaesthesia:** induction with 5 mg/kg IV thiopental sodium; maintenance: sevoflurane, 70% N_2O and 30% O_2 to MAC 1 **NMBA:** single intubating dose: rocuronium 0.8 mg/kg; maintenance dose: no information available **Comparison:** sugammadex 3 mg/kg (n = 45) vs neostigmine 30 µg/kg (n = 45) **Administration time of sugammadex or neostigmine:** reappearance of T2
Outcomes	Heart rate, mean systolic and diastolic blood pressures, and electrocardiographic alterations including QTc (QT Fredericia and QT Bazett) were recorded
Notes	**Publication type:** peer-reviewed article **Country:** Turkey **Conversions:** none **Handling of adverse events:** No discrepancy exists between AEs presented in the original article and those reported in this review **Authors' conclusions:** We suggest that sugammadex might be preferred, as it provides greater haemodynamics stability than is provided by the neostigmine-atropine combination to reverse rocuronium-induced neuromuscular blockade in cardiac patients undergoing non-cardiac surgery

Kizilay 2016 *(Continued)*

Contact: first trial author Deniz Kizilay contacted by email: denizkizilay@yahoo.com on 24.05.2016; replied 29.05

* Indicates unpublished data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by lots *
Allocation concealment (selection bias)	High risk	No allocation concealment *
Blinding of participants (performance bias)	Low risk	Participants were blinded *
Blinding of personnel (performance bias)	High risk	Personnel were not blinded *
Blinding of primary outcome assessment (detection bias)	High risk	TOF-watch assessor was not blinded *
Blinding of safety assessment (detection bias)	High risk	Safety assessor was not blinded *
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs: 90 participants were randomized, 45 to each group
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published article clearly includes all expected outcomes
Funding bias	Low risk	Study was funded by the first trial author *
Other bias	Unclear risk	No apparent other type of bias, except no information on sample size calculation. No significant differences between groups in terms of age, sex, weight, ASA-, NYHA- classification, or comorbid disorders, except coronary disease

Koc 2015

Methods	**Study design:** randomized, prospective, controlled trial **Sample size calculation:** no information available
Participants	**Number of randomized participants:** 33 **Inclusion criteria:** aged 18 to 65, ASA I to III, undergoing short-term (< 90 minutes) elective abdominal surgery (colectomy, incisional and umbilical hernia) **Exclusion criteria:** expected difficult intubation; receiving medication known to interact with rocuronium; neuromuscular disease, significant renal or liver disease, an allergy or other contraindication to medication used during the study; pregnancy;morbid obesity

Koc 2015 *(Continued)*

Interventions	**Anaesthesia:** induced with 1 to 2 µg/kg fentanyl, 5 to 7 mg/kg thiopental; maintained with 50% O_2-N_2O and 1% sevoflurane **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 0.1 to 0.2 mg/kg **Comparison:** sugammadex 2 mg/kg (n = 16) vs neostigmine 50 µg/kg + atropine 20 µg/kg (n = 17) **Administration time of sugammadex or neostigmine:** reappearance of T2
Outcomes	Time to recovery of TOFR > 0.9; efficacy and cost-effectiveness of sugammadex vs neostigmine
Notes	**Publication type:** peer-reviewed article **Country:** Turkey, 1 centre **Conversions:** none **Handling of adverse events:** No discrepancy exists between AEs presented in the original article and those reported in this review **Authors' conclusions:** Recovery of neuromuscular function after rocuronium to TOFR of 0.9 was faster with 2 mg/kg sugammadex than with 50 µg/kg neostigmine; sugammadex was more expensive than neostigmine **Contact:** corresponding trial author Guldem Turan contacted by e-mail: gturanmd@yahoo.com on 12.10.2015; no reply received **Language:** article in Turkish

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly divided"; no further information available
Allocation concealment (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of participants (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of personnel (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of primary outcome assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of safety assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published article clearly includes all expected outcomes
Funding bias	Unclear risk	Unable to assess owing to insufficient information

Koc 2015 *(Continued)*

Other bias	Unclear risk	Unable to assess owing to insufficient information

Kogler 2012

Methods	**Study design:** prospective, randomized study **Sample size calculation:** no information available
Participants	**Number of randomized participants:** 31 **Inclusion criteria:** adult; ASA IV; scheduled for procedures in interventional bronchoscopy **Exclusion criteria:** no information available
Interventions	**Anaesthesia:** induced with midazolam, propofol, and sufentanil; maintained with increments of propofol **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 0.15 mg/kg **Comparison:** sugammadex 2.0 mg/kg (n = 16) vs neostigmine 70 µg/kg (n = 15) **Administration time of sugammadex or neostigmine:** PTC 1 to 2
Outcomes	**Primary efficacy parameter:** time to recovery of TOFR to 0.9 **Other parameters:** time from beginning of anaesthesia to time of patient discharge to the PACU and blood gas analysis at time of discharge, adverse events
Notes	**Publication type:** meeting abstract **Country:** Croatia **Conversions:** none **Handling of adverse events:** No discrepancy exists between AEs presented in the original article and those reported in this review **Authors' conclusions:** Sugammadex provided significantly faster recovery time from rocuronium-induced profound neuromuscular block in comparison with neostigmine, and shorter duration from beginning of anaesthesia to patient discharge to PACU with lower values of $PaCO_2$ **Contact:** third trial author Maja Karaman Ilic contacted: mkilic@inet.hr on 13.10.2015; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized"; no further information
Allocation concealment (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of participants (performance bias)	Unclear risk	Unable to assess owing to insufficient information

Kogler 2012 *(Continued)*

Blinding of personnel (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of primary outcome assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of safety assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to assess owing to insufficient information
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published meeting abstract clearly includes all expected outcomes
Funding bias	Unclear risk	Unable to assess owing to insufficient information
Other bias	Unclear risk	Unable to assess owing to insufficient information

Koyuncu 2015

Methods	**Study design:** single-centre, randomized, double-blinded trial **Sample size calculation:** powered to detect a 0.5 difference between groups on 4-point PONV scale
Participants	**Number of randomized participants:** 100 **Inclusion criteria:** ASA I to II, scheduled for extremity surgery (tendon repair and skin graft surgery) during general anaesthesia **Exclusion criteria:** any contraindication to sugammadex or neostigmine administration; emergency or urgent procedures; BMI ≥27 kg/m^2, hepatic impairment (alanine aminotransferase or aspartate aminotransferase > 2 times normal), renal impairment (serum creatinine > 2 mg/dL)
Interventions	**Anaesthesia:** induced with propofol 2 to 2.5 mg/kg and fentanyl 1 µg/kg, maintained with 5% to 6% desflurane in 66% nitrous oxide in oxygen **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 0.15 mg/kg **Comparison:** sugammadex 2 mg/kg (n = 50) vs neostigmine 70 µg/kg + atropine 0.4 mg per 1 mg neostigmine (n = 50) **Administration time of sugammadex or neostigmine:** 4 twitches of TOF visible with fade
Outcomes	PONV, postoperative pain on VAS, clinical recovery parameters (extubation time, first eye opening, head-lift time, first flatus, first oral intake, ambulation), heart rate, non-invasive blood pressure, oxygen saturation, antiemetic consumption and side effects; bradycardia (heart rate < 60/min), hypotension (decrease in systolic arterial pressure < 10 mmHg from baseline), itching, headache, respiratory depression (respiratory rate < 10), cough, bronchospasm, irritation at injection site, abnormally increased oral secretions
Notes	**Publication type:** peer-reviewed article **Country:** Turkey **Conversions:** none

Koyuncu 2015 *(Continued)*

Handling of adverse events: No discrepancy exists between AEs presented in the original article and those reported in this review

Authors' conclusions: Non-depolarizing neuromuscular blocking antagonism with sugammadex speeds recovery of neuromuscular strength but only slightly and transiently reduces PONV compared with neostigmine and atropine

Contact: first trial author Onur Koyuncu contacted by e-mail: onurko@yahoo.com on 25.05.2016; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Web-based randomization; participants were "randomly assigned 1:1 without stratification"
Allocation concealment (selection bias)	Low risk	Central allocation (secondary to web-based randomization)
Blinding of participants (performance bias)	Unclear risk	"Double-blind study"; no further information available
Blinding of personnel (performance bias)	Unclear risk	"Double-blind study"; no further information available
Blinding of primary outcome assessment (detection bias)	Unclear risk	"Double-blind study"; no further information available
Blinding of safety assessment (detection bias)	Unclear risk	An anaesthetist blinded to treatment queried participants about postoperative pain using VAS; no further information available about blinding of assessor of other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs: 100 consenting patients who fulfilled entry criteria were enrolled; all completed the entire study and were included in the final analysis
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published article clearly includes all expected outcomes
Funding bias	High risk	Trial authors have no financial relationship with any organization. Supported by internal funds only. Department of Outcomes Research is supported by grants from Merck, and Dr Sessler has served on a Merck advisory board
Other bias	Low risk	Appears free of other sources of bias. Study sample size calculation designed to address this review's secondary outcome. Participants assigned to each medication comparable with respect to age, height, body weight, ASA physical status, Apfel score, duration of surgery, and duration of anaesthesia

Kvolik 2012a

Methods	**Study design:** prospective, randomized study **Sample size calculation:** no information available
Participants	**Number of randomized participants:** 36

Kvolik 2012a *(Continued)*

	Inclusion criteria: undergoing thyroidectomy **Exclusion criteria:** no information available
Interventions	**Anaesthesia:** propofol and fentanyl for both induction and maintenance **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 0.1 mg/kg **Comparison:** sugammadex 2 mg/kg (n = 17) vs neostigmine 50 µg/kg (n = 19) **Administration time of sugammadex or neostigmine:** reappearance of T2
Outcomes	Recovery of TOFR > 90% of baseline, recovery of cough reflexes enabling safe extubation, spontaneous minute volume at the time of extubation
Notes	**Publication type:** meeting abstract **Country:** Croatia **Conversions:** none **Handling of adverse events:** No discrepancy exists between AEs presented in the meeting abstract and those reported in this review **Authors' conclusions:** Recovery of cough reflexes was faster and respiration more efficient in patients receiving sugammadex. A safe extubation was determined by age, TOF recovery, and effects of other anaesthetics **Contact:** first trial author Slavica Kvolik contacted by email: slavica.kvolik@os.t-com.hr on 14.10.2015; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized"; no further information available
Allocation concealment (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of participants (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of personnel (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of primary outcome assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of safety assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to assess owing to insufficient information
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published meeting abstract clearly includes all expected outcomes

Kvolik 2012a *(Continued)*

Funding bias	Unclear risk	Unable to assess owing to insufficient information
Other bias	Unclear risk	No information on sample size calculation. No differences regarding participant characteristics and preparative FT_4, FT_3, and TSH levels between groups

Kvolik 2012b

Methods	**Study design:** prospective, randomized study **Sample size calculation:** no information available
Participants	**Number of randomized participants:** 24 **Inclusion criteria:** euthyroid, undergoing general anaesthesia for thyroidectomy **Exclusion criteria:** no information available
Interventions	**Anaesthesia:** propofol and fentanyl **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 0.1 mg/kg **Comparison:** neostigmine 50 µg/kg vs sugammadex 2 mg/kg **Administration time of sugammadex or neostigmine:** end of surgery
Outcomes	Thyroid hormones (FT_3, FT_4, and TSH) measured before surgery, 1 hour after reversal, and 24 hours after surgery
Notes	**Publication type:** meeting abstract **Country:** Croatia **Conversions:** none **Authors' conclusions:** Sugammadex treatment did not change levels of thyroid hormones and may be safely used in patients undergoing total thyroidectomy **Contact:** first trial author Slavica Kvolik contacted by e-mail: slavica.kvolik@os.t-com.hr on 24.05.2016; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized study"; no further information available
Allocation concealment (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of participants (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of personnel (performance bias)	Unclear risk	Unable to assess owing to insufficient information

Kvolik 2012b *(Continued)*

Blinding of primary outcome assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of safety assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to assess owing to insufficient information
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published meeting abstract clearly includes all expected outcomes
Funding bias	Unclear risk	Unable to assess owing to insufficient information
Other bias	Unclear risk	No information on sample size calculation. No differences regarding participant characteristics and drug consumption between groups

Kvolik 2013

Methods	**Study design:** prospective randomized study **Sample size calculation:** no information available
Participants	**Number of randomized participants:** 44 **Inclusion criteria:** adults, ASA I to III, undergoing thyroidectomy or breast cancer surgery **Exclusion criteria:** no information available
Interventions	**Anaesthesia:** induced with propofol 2 mg/kg and fentanyl 5 µg/kg; maintenance: no information available **NMBA:** single intubating dose: rocuronium 0.6 mg/kg **Comparison:** sugammadex 2 mg/kg (n = 20) vs neostigmine 50 µg/kg + atropine 25 µg/kg (n = 24) **Administration time of sugammadex or neostigmine:** reappearance of T2
Outcomes	Time to recovery of TOF 90% and mean increase in BIS indices per each minute after reversal
Notes	**Publication type:** meeting abstract **Country:** Croatia **Conversions:** none **Authors' conclusions:** An increase in BIS index registered after reversal of rocuronium effects was faster during the recovery period among patients who were given sugammadex rather than neostigmine. Although a rapid increase in BIS indices was registered in the sugammadex group, more sensitive measurements are needed to confirm the clinical value of this observation **Contact:** first trial author Slavica Kvolik contacted by e-mail: slavica.kvolik@os.t-com.hr on 14.10.2015; no reply received
Risk of bias	

Kvolik 2013 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Allocation concealment (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of participants (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of personnel (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of primary outcome assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of safety assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to assess owing to insufficient information
Selective reporting (reporting bias)	Unclear risk	Study protocol not available, but published meeting abstract clearly includes all expected outcomes
Funding bias	Unclear risk	Unable to assess owing to insufficient information
Other bias	Unclear risk	Unable to assess owing to insufficient information

Lemmens 2010

Methods	**Study design:** multi-centre, randomized, parallel-group, safety assessor-blinded, phase 3a trial (SIGNAL study) **Sample size calculation:** powered to detect a difference of 5 minutes in time to recovery of TOFR to 0.9
Participants	**Number of randomized participants:** 94 **Inclusion criteria:** adults > 18 years, ASA I to IV, scheduled to undergo elective surgery in the supine position under general anaesthesia requiring use of a neuromuscular blocking agent for tracheal intubation and maintenance of neuromuscular block **Exclusion criteria:** neuromuscular disorder; history of malignant hyperthermia; significant renal dysfunction; allergy to narcotics, muscle relaxants, or other medication used during general anaesthesia; using medication known to interfere with neuromuscular blocking agents (e.g. antibiotics, anticonvulsants, magnesium); or pregnant, breastfeeding, or of childbearing potential and not using an adequate method of contraception
Interventions	**Anaesthesia:** induced with intravenous opioid and propofol; maintained with intravenous opioid and sevoflurane **NMBA:** single intubating dose: vecuronium 0.1 mg/kg; maintenance dose: vecuronium 0.015 mg/kg

Lemmens 2010 *(Continued)*

	Comparison: sugammadex 4.0 mg/kg (n = 52) vs neostigmine 70 µg/kg + 14 µg/kg glycopyrrolate (n = 42) **Administration time of sugammadex or neostigmine:** reappearance of PTC 1 to 2
Outcomes	**Primary efficacy variable:** time from start of administration of Org 25969/neostigmine to recovery T4/T1 ratio to 0.9 **Secondary efficacy variables:** time from start of administration of Org 25969/neostigmine to recovery T4/T1 ratio to 0.7 and 0.8; assessment of clinical signs of recovery (level of consciousness, 5 second head-lift, general muscle weakness) **Safety analysis:** adverse events, serious adverse events, laboratory data, vital signs
Notes	**Publication type:** peer-reviewed article **Country:** USA, 9 centres **Handling of adverse events:** Data presented in "Clinical signs of recovery" section (page 7) regarding number of participants with general muscle weakness and number not able to perform 5 second head-lift were considered to show adverse events in this review and were counted as such **Conversions:** none **Authors' conclusions:** Sugammadex provided effective and rapid reversal of profound neuromuscular block induced by vecuronium under sevoflurane anaesthesia **Contact:** first trial author Hendrikus JM Lemmens contacted by email: hlemmens@stanford.edu; replied referring to Merck, but did not supply contact email address at Merck

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomization schedule prepared centrally by the study sponsor"
Allocation concealment (selection bias)	Low risk	Central allocation (secondary to central randomization)
Blinding of participants (performance bias)	High risk	Open-label study; no further information available
Blinding of personnel (performance bias)	High risk	Open-label study; no further information available
Blinding of primary outcome assessment (detection bias)	High risk	Open-label study; no further information available
Blinding of safety assessment (detection bias)	Low risk	Only safety assessor was blinded. Drugs were prepared by an investigator who was not involved in safety assessments
Incomplete outcome data (attrition bias) All outcomes	High risk	Imbalance in distribution: After interim analysis and recommendation by the Data and Safety Monitoring Board, the neostigmine group was discontinued because of marked differences in efficacy between treatments, although by this time, 42 participants had already been randomized into the neostigmine group. A total of 11 participants (5 sugammadex and 6 neostigmine) discontinued the trial before receiving the study drug. In addition, 1 participant randomized to vecuronium and sugammadex received rocuronium plus neostigmine and was excluded from the all-subjects-treated population, but was

Lemmens 2010 *(Continued)*

		included in the intent-to-treat population according to the randomization schedule. Therefore, the all-subjects-treated population consisted of 46 participants treated with sugammadex and 36 treated with neostigmine, and the intent-to-treat population consisted of 47 participants randomized to sugammadex and 36 randomized to neostigmine
Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrials.gov (NCT00473694), and all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way
Funding bias	High risk	Study was funded by Merck Research Laboratories, Summit, New Jersey, USA. Hendrikus Lemmens has participated in a Merck advisory board. Jovino Ben Morte is an employee of Merck Research Laboratories, Summit, New Jersey, USA. Mohammad El-Orbany has received research funding from Merck. James Berry and Gavin Martin declare that they have no other competing interests
Other bias	High risk	Study sample size calculation designed to address this review's primary outcome. One intervention group was discontinued owing to marked differences in efficacy between groups after interim analysis

Martini 2014

Methods	**Study design:** randomized blinded study (BLISS trial) **Sample size calculation:** based on the expectation of the surgeon for distribution of surgical ratings between moderate and deep neuromuscular block
Participants	**Number of randomized participants:** 26 **Inclusion criteria:** scheduled to undergo an elective laparoscopic prostatectomy or nephrectomy (partial or total) who have given written consent **Exclusion criteria:** ASA class > III, age < 18 years, inability to give informed consent, known or suspected neuromuscular disease, allergy to medication to be used during anaesthesia, (family) history of malignant hyperthermia, renal insufficiency (serum creatinine > 2 times normal, urine output < 0.5 mL/kg/h, glomerular filtration rate < 60 mL/h, or proteinuria), previous retroperitoneal surgery, body mass index ≥ 35 kg/m^2
Interventions	**Anaesthesia:** propofol and sufentanil **NMBA:** single intubating dose: atracurium 0.5 mg/kg (for moderate NMB) or rocuronium 1.0 mg/kg (for deep NMB); maintenance dose: mivacurium 0.5 mg/kg/h (for moderate NMB) or rocuronium 0.6 mg/kg/h (for deep NMB) **Comparison:** neostigmine 1 to 2 mg + atropine 0.5 to 1 mg (for reversal of moderate NMB) (n = 12) vs sugammadex 4 mg/kg (for reversal of deep NMB) (n = 12) **Administration time of neostigmine or sugammadex:** reappearance of T2 or PTC 1 to 2
Outcomes	**Primary endpoint:** influence of the depth of NMB on the SRS (surgical rating score) **Secondary endpoints:** (1) assessment of the level of agreement between anaesthetists and surgeon in terms of their rating of surgical conditions, (2) effects of level of NMB on haemodynamic variables during surgery, time to TOFR.= 0.9, and relevant variables in the PACU (pain rating, sedation levels, and cardiorespiratory variables)
Notes	**Publication type:** peer-reviewed article **Country:** Netherlands

Martini 2014 *(Continued)*

Conversions: none

Authors' conclusions: Application of the 5-point SRS showed that deep NMB results in improved quality of surgical conditions compared with moderate block in retroperitoneal laparoscopies, without compromise to patients' perioperative and postoperative cardiorespiratory conditions

Contact: first trial author A. Dahan contacted by e-mail: a.dahan@lumc.nl on 27.05.2016; replied on 27.05.16
* Indicates unpublished data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed using a computer-generated randomization code
Allocation concealment (selection bias)	Unclear risk	Sealed, opaque, and sequentially numbered envelopes with codes were presented to the attending anaesthetist who prepared the medication and took care of participant dosing during anaesthesia *
Blinding of participants (performance bias)	Low risk	Participants were under general anaesthesia and therefore were blinded
Blinding of personnel (performance bias)	High risk	Attending anaesthesiologist was not blinded; the surgical team, the research team, and the anaesthetist who scored the video were all blinded
Blinding of primary outcome assessment (detection bias)	Low risk	TOF measurements were performed by a fully blinded researcher or research nurse *
Blinding of safety assessment (detection bias)	Low risk	PACU evaluation (pain, sedation, cardiovascular variables) was performed by a fully blinded researcher or research nurse *
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants are accounted for, and missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups: A total of 30 patients were screened. Four patients met 1 or more exclusion criteria. The others were randomized. Two patients withdrew consent before treatment, resulting in 12 participants in each group
Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrials.gov (NCT01631149), and all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way
Funding bias	High risk	L.P.A. and A.D. received speaker fees from Merck BV, Oss, The Netherlands. This study is supported in part by Merck BV, Oss, The Netherlands, and by institutional funds from the Department of Anaesthesiology, Leiden University Medical Centre, Leiden, The Netherlands. Merck was not involved in the design and conduct of the study, data analysis, and production of the manuscript. Merck's statistician Hein Fennema assisted with sample size analysis
Other bias	High risk	Study sample size calculation not designed to address this review's primary or secondary outcomes. The 2 treatment groups were similar in physical characteristics, gender, types of surgery, and haemodynamic variables

Mekawy 2012

Methods	**Study design:** randomized, controlled study **Sample size calculation:** no information available
Participants	**Number of randomized participants:** 40 **Inclusion criteria:** age 20 to 45, ASA I to II, with chronic sinuitis undergoing endoscopic sinus surgery with or without seroplasty **Exclusion criteria:** cardiovascular system pathology, coagulation defects, bronchial asthma, COPD, muscle disease or neuromuscular disorder, renal or hepatic disease, taking any drugs that affect renal function or blood coagulation, history of difficult intubation or suspected to be difficult
Interventions	**Anaesthesia:** induced with: propofol 2 to 2.5 mg/kg and fentanyl 1 µg/kg. Maintained with 50% oxygen in air and isoflurane to MAC 1.5. Hypotensive anaesthesia was used to maintain MAP 50 to 60 mmHg **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 0.10 to 0.15 mg/kg **Comparison:** sugammadex 4 mg/kg (n = 20) vs neostigmine 50 µg/kg + atropine 20 µg/kg (n = 20) **Administration time of sugammadex or neostigmine:** reappearance of T2
Outcomes	Time from administration of study drug until TOFR of 0.9, assessment of postoperative respiratory complications using the Postoperative Respiratory System Evaluation Score (PRSES) at 1 and 5 minutes after extubation
Notes	**Publication type:** peer-reviewed article **Country:** Egypt **Conversions:** none **Handling of adverse events:** Data presented in Table 4 - "Incidence of postoperative respiratory complications using PRSES score: PRESES 2 and PRSES 3-5 at 1 minute" - as well as data regarding number of participants not able to perform 5 second head-lift (presented on page 177) were considered as adverse events in this review and were counted as such **Authors' conclusions:** Use of sugammadex in reversing rocuronium-induced neuromuscular block among patients undergoing functional endoscopic surgery is superior to use of neostigmine. Additional studies are required to weigh the cost-benefit relationship of the use of sugammadex in routine clinical practice **Contact:** corresponding trial author E.A. Fouad Ali contacted by e-mail: Mhz_home@hotmail.com on 16.10.2015; has not replied

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated system"
Allocation concealment (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of participants (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of personnel (performance bias)	Low risk	Study drugs were prepared in identical 10 mL syringes and were injected by a resident who was blinded to the drug injected

Mekawy 2012 *(Continued)*

Blinding of primary outcome assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of safety assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants are accounted for, and missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups: A total of 54 participants consented to participate in this study, and all were ASA I and II. Nine patients were excluded because they did not meet the inclusion criteria, and 5 were withdrawn from the study owing to inability to apply the study protocol; these 5 patients had BIS readings higher than 60 before the reversal drug injection that mandates reopening of inhalational agents; this violates the study protocol
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published article clearly includes all expected outcomes
Funding bias	Unclear risk	Unable to assess owing to insufficient information
Other bias	Unclear risk	No apparent other types of bias, except no information on sample size calculation. No significant differences regarding demographic characteristics, surgery, isoflurane consumption, nitroglycerin requirements, rocuronium supplemented, and intraoperative blood loss among the 2 groups

Pongracz 2013

Methods	**Study design:** single-centre, randomized, controlled, double-blind, 4 groups parallel-arm study **Sample size calculation:** powered to detect a 300 second decrease in time of recovery to TOFR > 0.9
Participants	**Number of randomized participants:** 80 **Inclusion criteria:** aged 18 to 65 years, body mass index 18.5 to 25.0 kg/m^2, ASA I to III, scheduled for elective surgery with an expected duration > 50 minutes under general anaesthesia with intubation of the trachea **Exclusion criteria:** participated in another clinical trial within 1 month, suspected difficult airway, bronchial asthma, chronic obstructive pulmonary disease, known NM disease, suspected malignant hyperthermia, hepatic or renal dysfunction, glaucoma, allergy to medication used in this trial, taking medicaments that might influence the effect of NMB agents, pregnant or breastfeeding
Interventions	**Anaesthesia:** induced with intravenous propofol (1.5 to 2.5 mg/kg) and fentanyl (2 µg/kg) and maintained with inhaled sevoflurane (1.1 to 1.8 vol %) in air–oxygen mixture and intravenous fentanyl according to clinical need **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 0.1 to 0.15 mg/kg **Comparison:** sugammadex 0.5 mg/kg (n = 19), 1.0 mg/kg (n = 20), 2.0 mg/kg (n = 20), and neostigmine 0.05 mg/kg + atropine 0.015 mg/kg (n = 16) **Administration time of sugammadex or neostigmine:** reappearance of T4 at 3 consecutive TOF measurements
Outcomes	**Primary endpoint:** rapid reversal (≤ 2.0 minutes average, upper limit of 5.0 minutes)

Pongracz 2013 *(Continued)*

	Secondary endpoint: slower reversal (≤ 5.0 minutes average, upper limit of 10 minutes)
Notes	**Publication type:** peer-reviewed article **Country:** Hungary **Conversions:** none **Handling of adverse events:** No discrepancy exists between AEs presented in the original article and those reported in this review **Authors' conclusions:** Sugammadex 1.0 mg/kg rapidly and effectively reverses rocuronium-induced block that has recovered spontaneously to a threshold TOF count four. A dose of 0.5 mg/kg was equally effective, but satisfactory antagonism took as long as 8 minutes to take place **Contact:** corresponding trial author Bela Fülesdi contacted by email: fulesdi@dote.hu on 28.02.2016; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted-block randomization. Ten numbers of 1 to 4 were prepared 20 times each and were placed into an envelope; each number identified 1 of the 4 study groups
Allocation concealment (selection bias)	Unclear risk	Envelopes were used; no information on whether they were sealed, opaque, and sequentially numbered
Blinding of participants (performance bias)	Low risk	In the operating room, a different anaesthesiologist prepared the study drug in an unlabelled syringe according to randomization and injected it upon request of the blinded anaesthesiologist who was responsible for the participant
Blinding of personnel (performance bias)	Low risk	In the operating room, a different anaesthesiologist prepared the study drug in an unlabelled syringe according to randomization and injected it upon request of the blinded anaesthesiologist who was responsible for the participant
Blinding of primary outcome assessment (detection bias)	Unclear risk	No information on identity of blinding or of TOF-watch assessor
Blinding of safety assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants are accounted for, and missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups: Study drugs were injected in 80 participants; 5 were excluded. In 4 participants, the TOFR did not reach 1.0 within 15 minutes after injection of neostigmine; therefore 2 mg/kg of sugammadex was given as rescue medication to prevent RPONB. In 1 patient (0.5 mg/kg sugammadex group), the study drug was injected at a TOFR of 0.6 (minor protocol violation). With 5 participants excluded from the final efficacy analysis, 75 participants were finally analysed for TOF recovery
Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrialsregister.eu (EudraCT Number: 2011-001683-22), and all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way
Funding bias	Unclear risk	Unable to assess owing to insufficient information

Pongracz 2013 *(Continued)*

Other bias	Low risk	Appears free of other sources of bias. Study sample size calculation designed to address this review's primary outcome

Rahe-Meyer 2014

Methods	**Study design:** randomized, parallel-group, double-blind trial **Sample size calculation:** powered to address the primary endpoint (bleeding events)
Participants	**Number of randomized participants:** 1198 **Inclusion criteria:** adults (≥ 18 years of age) of ASA class I to III undergoing joint (hip or knee) replacement surgery/revision or intracapsular or extracapsular hip fracture surgery, and planned to receive thrombose-prophylaxis and neuromuscular blockade with rocuronium or vecuronium **Exclusion criteria:** suspected anatomical malformations that could make endotracheal intubation more difficult; neuromuscular disorders that might affect neuromuscular blockade; medical history of coagulation disorder, bleeding diathesis, systemic lupus erythematosus, or antiphospholipid syndrome; history or evidence of active abnormal bleeding or blood clotting (e.g. thrombosis) within 30 days before screening; severe hepatic dysfunction; active hip or knee infection scheduled for revision surgery; known or suspected severe renal insufficiency (estimated creatinine clearance < 30 mL/min); family history of malignant hyperthermia; morbid obesity (body mass index > 35); hypersensitivity to or conditions that would contraindicate the use of sugammadex, muscle relaxants or their excipients, or other medication(s) used during general anaesthesia; receiving treatment with toremifene and/or fusidic acid intravenously within 24 hours before or after study medication administration because of potential drug–drug interaction; previously treated with sugammadex, participated in a previous sugammadex trial, or participated in another clinical trial within 30 days of this trial; pregnant or breast-feeding
Interventions	**Anaesthesia:** induction and maintenance according to usual practice at the site **NMBA:** rocuronium or vecuronium, according to usual practice at the site **Comparison:** sugammadex 4 mg/kg (n = 596) vs usual care (neostigmine with glycopyrrolate or atropine, or placebo/spontaneous recovery) (n = 588) **Administration time of sugammadex, neostigmine, or placebo:** not stated
Outcomes	**Primary endpoint:** proportion of participants with ≥ 1 adjudicated event of bleeding that occurred within 24 hours after trial medication administration **Key secondary endpoints:** change from baseline in aPTT at 10 and 60 minutes after trial medication administration **Additional endpoints:** postoperative drainage volumes within first 24 hours after trial medication administration; rates of postoperative transfusion (initiated after sugammadex or placebo/neostigmine was given) and respective transfusion volumes; postoperative changes in haemoglobin based on the bleeding index; incidence of anaemia with onset within 72 hours after administration of trial medication **Safety assessment:** adverse events and serious adverse events
Notes	**Publication type:** peer-reviewed article **Country:** Austria, Belgium, and Germany (22 centres) **Conversions:** none **Authors' conclusions:** Sugammadex produced limited, transient (< 1 hour) increases in aPTT and PT but was not associated with increased risk of bleeding vs usual care

Rahe-Meyer 2014 *(Continued)*

Contact: first trial author Niels Rahe-Meyer contacted by email: rahe-meyer.niels@mh-hannover.de on 28.03.2016; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralized interactive voice and Web response system
Allocation concealment (selection bias)	Low risk	Central allocation (secondary to central randomization)
Blinding of participants (performance bias)	Low risk	Participants were blinded
Blinding of personnel (performance bias)	Low risk	Trial medication was administered in a blinded manner by the anaesthesiologist after preparation in an unblinded manner by the pharmacist. To further maintain blinding, opaque, coloured syringes were used to mask potential differences in the tint of study treatments
Blinding of primary outcome assessment (detection bias)	Low risk	Not relevant as TOF-watch assessment was not reported in this study
Blinding of safety assessment (detection bias)	Low risk	Initial determination was made by a blinded safety assessor on site, who was a medically qualified member of the surgical team. For all bleeding events thus identified, available medical information was submitted for adjudication to the independent, blinded Primary Adjudication Committee, consisting of external experts in the field
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants are accounted for, and missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups: Of 1198 participants randomized, 1184 were treated (sugammadex n = 596, usual care n = 588) from October 2011 to September 2012. A total of 52% of usual care participants received neostigmine, and 48% underwent spontaneous recovery. Overall, 1137 participants completed the trial: 575 (96.5%) in the sugammadex group and 562 (95.6%) in the usual care group
Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrials.gov (NCT01422304), and all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way
Funding bias	High risk	Authors Fennema, Speek, McCrary Sisk, Williams-Herman, Woo, and Szegedi are current or former employees of subsidiaries of Merck & Co., Inc. (Whitehouse Station, New Jersey), and may own stock or hold stock options in the company. Dr. Rahe-Meyer reports receiving honoraria for advisory board membership, lectures, and/or consultancy for CSL-Behring (King of Prussia, Pennsylvania) and Merck (Whitehouse Station, New Jersey). His institution received a grant for the study. Dr. Wulf reports receiving honoraria for advisory board memberships from Boehringer Ingelheim (Ingelheim, Germany), Sintectica (Canton Ticino, Switzerland), and Carefusion (San Diego, California), and for lectures or consultancy from Teleflex (Wayne, Pennsylvania), Sintetica (Canton Ticino, Switzerland), Vygon (Landsdale, Pennsylvania), B. Braun Medical Inc. (Melsungen, Germany), Pajunk GmbH (Geisingen, Germany), SonoSite Inc. (Bothell, Washington), and Merck (Whitehouse Station, New Jersey). Dr. Blobner reports receiving fees from Merck (Whitehouse Station, New Jersey) for consulting, lectures, advisory board membership, and participation in reviews and

Rahe-Meyer 2014 *(Continued)*

		committees. He reports that his institution received grants and money for travel related to the study from Merck (Whitehouse Station, New Jersey). Dr. Schulman reports receiving travel support from Merck (Whitehouse Station, New Jersey) for investigators' meetings and an honorarium for work on the Adjudication Committee. Dr. Przemeck reports receiving travel support from Merck (Whitehouse Station, New Jersey) for investigators' meetings. His institution received a grant for patient visits and other costs associated with the study. Dr. Klimscha reports his institution received funds from Merck (Whitehouse Station, New Jersey) associated with the study
Other bias	Low risk	Appears free of other sources of bias. Study sample size calculation designed to address this review's secondary outcome. Baseline characteristics similar across treatment groups

Raziel 2013

Methods	**Study design:** prospective, single-centre, double-arm study **Sample size calculation:** no information available
Participants	**Number of randomized participants:** 40 **Inclusion criteria:** morbidly obese male or female patients aged 20 to 65 years who are candidates for bariatric surgery, can read and understand the fundamental nature of the clinical protocol, and must sign the Informed Consent Form **Exclusion criteria:** treated with drugs that might interact with rocuronium; history of malignant hyperthermia or significant renal disease; known allergy to one of the drugs used during anaesthesia; known muscular disease; severe cardiovascular disease (NYHA > 2); breastfeeding; refusing to follow the clinical protocol; participating in a different clinical trial; refusing to sign the Informed Consent Form; physician's objection
Interventions	**Anaesthesia:** no information available **NMBA:** single intubating dose: rocuronium 0.4 mg/kg; maintenance dose: rocuronium 0.1 to 0.2 mg/kg (not more than × 2) **Comparison:** sugammadex 2 mg/kg (n = 21) vs neostigmine 50 µg/kg + atropine 10 µg/kg (n = 19) **Administration time of sugammadex or neostigmine:** reappearance of T2
Outcomes	**Primary outcome measures:** safety of sugammadex reversal - number of drug-related adverse events with sugammadex vs neostigmine, monitoring of neuromuscular reaction from end of anaesthesia recovery (in the OR) until participant is released from hospital (48 to 72 hours post surgery) **Secondary outcome measures**: use of sugammadex for neuromuscular anaesthesia reversal; higher patient satisfaction compared with neostigmine, monitoring of neuromuscular reaction from end of anaesthesia recovery (in the OR) until participant is released from hospital (48 to 72 hours post surgery)
Notes	**Publication type:** meeting abstract **Country:** Israel **Conversions:** none **Authors' conclusions:** Sugammadex facilitates reversal of neuromuscular blockade after bariatric surgery, depending on depth of neuromuscular blockade induced **Contact:** first trial author Asnat Raziel contacted by e-mail: drraziel@zahav.net.il

Raziel 2013 *(Continued)*

* Indicates unpublished data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was done by the anaesthesiologist at the end of surgery and when 2 responses were achieved on TOF stimulation with computer randomization software, when 1 of the study drugs was administered *
Allocation concealment (selection bias)	Low risk	Adeqaute allocation concealment secondary to the randomization method
Blinding of participants (performance bias)	Low risk	Participants were blinded *
Blinding of personnel (performance bias)	High risk	Anaesthesiologists were not blinded; surgeons were blinded *
Blinding of primary outcome assessment (detection bias)	High risk	TOF-watch assessor was not blinded *
Blinding of safety assessment (detection bias)	Low risk	Safety assessor was blinded *
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs *
Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrials.gov (NCT01631396), and all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way
Funding bias	Low risk	Study was funded by internal sources for the hospital. Sugammadex was received FOC by manufacturer. Manufacturer was not involved at any stage of the study *
Other bias	Unclear risk	No apparent other type of bias, except no information on sample size calculation

Riga 2014

Methods	**Study design:** prospective, randomized, double-blinded trial **Sample size calculation:** no information available
Participants	**Number of randomized participants:** 114 **Inclusion criteria:** age > 40, ASA I to III, received general anaesthesia for elective surgery, with written consent **Exclusion criteria:** neurological, vascular, orthopaedic, or cardiac surgery; known psychiatric disorder or disease of the CNS; history of craniotomy; receiving tranquillisers or antidepressants on a regular basis preoperatively; alcoholism or drug dependence; history of stroke; refusal of patient; inability to read or write; MMSE < 22 preoperatively

Riga 2014 *(Continued)*

Interventions	**Anaesthesia:** induced and maintained with propofol, fentanyl/remifentanil, and sevoflurane **NMBA:** rocuronium; no information available on dose **Comparison:** sugammadex vs neostigmine/atropine; no information available on dose **Administration time of sugammadex or neostigmine:** reappearance of T2 in TOF sequence
Outcomes	**Primary outcome:** cognitive function assessed by change in MMSE, clock drawing test, and Isaac's set test, performed preoperatively, 1 hour postoperatively, and at discharge (1 to 15 days postoperatively)
Notes	**Publication type:** meeting abstract **Country:** Greece **Conversions:** none **Sample size calculation:** no information available **Authors' conclusions:** No significant difference was observed regarding cognitive function after neostigmine/atropine combination or sugammadex was received for reversal of rocuronium-induced neuromuscular blockade for elective surgery **Contact:** corresponding trial author Chrysanthi Batistaki contacted by email: chrysabatistaki@yahoo.gr; replied 17.05.2016 * Indicates unpublished data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-based randomization" *
Allocation concealment (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of participants (performance bias)	Low risk	Participants were blinded
Blinding of personnel (performance bias)	High risk	Other personnel were not blinded
Blinding of primary outcome assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of safety assessment (detection bias)	Low risk	Outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Five drop-outs due to intensive sedation postoperatively and inability to perform the MMSE 1 hour postoperatively *
Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrials.gov (NCT02419352), and all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way
Funding bias	Low risk	Study was not funded *

Riga 2014 *(Continued)*

Other bias	Unclear risk	No apparent other type of bias, except no information on sample size calculation

Sabo 2011

Methods	**Study design:** multi-centre, randomized, parallel-group, safety assessor-blinded and anaesthesiologist TOF-watch-blinded phase 4 study (Lightspeed study) **Sample size calculation:** based on anticipated difference in time to recovery to TOFR > 0.9, assuming that tracheal extubation would occur 2 to 3 minutes after sugammadex administration and 2 to 12 minutes after neostigmine administration
Participants	**Number of randomized participants:** 106 **Inclusion criteria:** adults aged ≥ 18 years and ≤ 65 years, ASA class I to III and scheduled to undergo elective open abdominal surgery under general anaesthesia, requiring use of an NMBA, in a position that would not interfere with use of the TOF-watch SX **Exclusion criteria:** neuromuscular disorder that complicated NMB assessment; history of malignant hyperthermia; significant renal (creatinine clearance < 30 mL/min) or hepatic dysfunction; allergy to opioids, muscle relaxants, or other medications used during general anaesthesia; pregnant, breast-feeding, or of childbearing potential and not using an adequate method of contraception
Interventions	**Anaesthesia:** induced with intravenous (IV) propofol, opioids, and/or nitrous oxide, and maintained with sevoflurane, IV opioids, and/or nitrous oxide with oxygen **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 0.15 mg/kg **Comparison:** sugammadex 4.0 mg/kg (n = 54) vs neostigmine 0.05 mg/kg + glycopyrrolate 0.01 mg/kg (n = 52) **Administration time of sugammadex or neostigmine:** time when the TOF-blinded anaesthesiologist considered participant ready for NMB reversal, but could ask the TOF-watch operator whether the participant recovered to at least PTC 1 to 2
Outcomes	**Primary efficacy variable:** incidence of residual NMB at time of tracheal extubation **Secondary efficacy variables:** time from study drug administration to recovery of TOFR to 0.7, 0.8, and 0.9 **Safety assessment:** all adverse events (AEs), serious adverse events (SAEs), vital signs
Notes	**Publication type:** peer-reviewed article **Country:** United States **Conversions:** none **Handling of adverse events:** No discrepancy exists between AEs presented in the original article and those reported in this review **Authors' conclusions:** Significantly more sugammadex-treated participants recovered to a TOFR ≥ 0.9 at extubation and did so significantly faster than neostigmine-treated participants. This study confirms that sugammadex is more effective than neostigmine in reducing potential for residual blockade in the absence of objective NMB monitoring **Contact:** corresponding author Daniel Sabo contacted by email: sabodp@anes.upmc.edu on 01.10.2016; no reply received

Sabo 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Web randomization system prepared centrally by study sponsor, whereby participants were randomly allocated to receive sugammadex or neostigmine in 1:1 ratio
Allocation concealment (selection bias)	Low risk	Central allocation (secondary to central randomization)
Blinding of participants (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of personnel (performance bias)	High risk	Anaesthesiologists were not blinded to study drug, as they needed to be able to adjust the anaesthetic regimen according to treatment group, but they were blinded to the specific depth of NMB based on TOF-watch recording at administration of reversal agent and degree of neuromuscular recovery at tracheal extubation
Blinding of primary outcome assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of safety assessment (detection bias)	Low risk	Safety assessor was blinded to treatment group and did not observe preparation of trial medication
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients are accounted for, and missing outcome data are balanced in numbers across intervention groups (Figure 1): A total of 106 participants were randomized (54 in the sugammadex group and 52 in the neostigmine group), of whom 100 received treatment (sugammadex n = 51, neostigmine n = 49). Three participants from the sugammadex group were discontinued for the following reasons: pretreatment adverse event n = 1; participant withdrew consent n = 1; and did not fulfil inclusion/exclusion criteria n = 1. Three participants were excluded from the neostigmine group for the following reasons: did not fulfil inclusion/exclusion criteria n = 1; TOF-watch difficulties n = 1; participant discharged before assessments n = 1. Three participants in the neostigmine group did not undergo efficacy assessments, thus the ITT group comprised 97 participants in total
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published article clearly includes all expected outcomes
Funding bias	High risk	Study was supported by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ
Other bias	Low risk	Appears free of other sources of bias. Study sample size calculation designed to address this review's primary outcome. Participant demographics well balanced between treatment groups

Schaller 2010

Methods	**Study design:** single-centre, randomized, parallel-group, double-blinded study (SUNDRO) **Sample size calculation:** no information available

Schaller 2010 *(Continued)*

Participants	**Number of randomized participants:** 99 **Inclusion criteria:** informed written consent, age 18 to 65 years, ASA I to III, scheduled for elective surgery under general anaesthesia with rocuronium for tracheal intubation **Exclusion criteria:** expected to have a difficult airway; known neuromuscular disease; significant hepatic or renal dysfunction; family history of malignant hyperthermia; known allergy to 1 of the drugs used in this protocol; intake of any medication that might interact with muscle relaxants; pregnant or breastfeeding; participated in another clinical study in the past 30 days
Interventions	**Anaesthesia:** induced with propofol (2 to 3 mg/kg) and fentanyl (0.1 to 0.2 µg/kg), maintained with propofol and remifentanil according to clinical need and anaesthesiologist preference **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 0.1 to 0.2 mg/kg **Comparison:** sugammadex 0.0625 mg/kg (n = 9), 0.125 mg/kg (n = 9), 0.25 mg/kg (n = 9), 0.5 mg/kg (n = 9), or 1.0 mg/kg (n = 9); or neostigmine 5 µg/kg (n = 9), 8 µg/kg (n = 9), 15 µg/kg (n = 9), 25 µg/kg (n = 9), or 40 µg/kg (n = 9) in a mixture with 1 µg glycopyrrolate/5 µg neostigmine or saline (n = 9) **Administration time of sugammadex, neostigmine, or placebo:** TOFR = 0.5
Outcomes	**Primary endpoint:** dose of sugammadex or neostigmine to accelerate time between start of administration of the respective study drug at a TOFR of 0.5 to a TOFR ≥ 0.9 in an average of 2 minutes, with an upper limit of 5 minutes for 95% of participants **Secondary endpoints:** doses of sugammadex and neostigmine for slower acceleration of reversal (i.e. average time of 5 minutes with upper limit of 10 minutes for 95% of participants) **Safety assessment:** adverse events and severe adverse events
Notes	**Publication type:** peer-reviewed article **Country:** Germany **Conversions:** none **Handling of adverse events:** More detailed information regarding number of adverse events possibly, probably, or definitely related to study drug was provided by trial authors through email correspondence; we used these updated numbers in the review **Authors' conclusions:** Sugammadex 0.22 mg/kg can reverse a TOFR of 0.5 to 0.9 or higher in an average time of 2 minutes. Within 5 minutes, 95% of patients reach this TOFR. Neostigmine 34 µg/kg can reverse a TOFR of 0.5 **Contact:** corresponding trial author Manferd Blobner contacted by email: blobner@l-rz.tu-muenchen.de on 15.03.2016; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomization list"
Allocation concealment (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of participants (performance bias)	Low risk	Participants were blinded
Blinding of personnel (performance bias)	Low risk	In the operating room, an additional anaesthesiologist prepared study drug according to participant number on the randomization list in an unlabelled sy-

Schaller 2010 *(Continued)*

		ringe. Upon request of the blinded anaesthesiologist responsible for the participant, study drug was injected
Blinding of primary outcome assessment (detection bias)	Low risk	Outcome assessor was blinded
Blinding of safety assessment (detection bias)	Low risk	Safety assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants are accounted for, but missing outcome data are not balanced in numbers across intervention groups, and it remains unclear whether missing outcome data are due to attrition or exclusion: Study drug was injected in 99 participants. In 5 participants, major protocol violations occurred: in 1 participant, neostigmine was incompletely injected as a result of a leaking venous cannula; and in 4 participants, electromyographic response was unstable (1 each in 5, 8, and 40 µg/kg neostigmine groups; 2 in 0.125 mg/kg sugammadex group). Because these violations might have affected primary and secondary endpoints, respective participant data were omitted, resulting in a per-protocol population of 94 participants
Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrials.gov (NCT00895609) and EudraCT (2008-008239-27); all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way
Funding bias	High risk	Support was provided solely from institutional and/or departmental sources. Drs. Blobner and Fink have received honoraria and travel grants from Schering-Plough, Inc. (Kenilworth, New Jersey), although this work was not sponsored by Schering-Plough in any way
Other bias	Unclear risk	No apparent other type of bias, except no information on sample size calculation. Groups did not differ significantly regarding sex, age, weight, height, and ASA physical status

Sherman 2014

Methods	**Study design:** prospective, randomized study **Sample size calculation:** no information available
Participants	**Number of randomized participants:** 57 **Inclusion criteria:** undergoing laparoscopic sleeve gastrectomy **Exclusion criteria:** no information available
Interventions	**Anaesthesia:** no information available **NMBA:** no information available **Comparison:** sugammadex 2 mg/kg (n = 32) vs neostigmine 2.5 mg (n = 25) **Administration time of sugammadex or neostigmine:** completion of surgery
Outcomes	**Postoperative complications:** critical respiratory events, pulmonary complications, minimum SpO_2 values in the PACU, airway and pulmonary morbidity, unexpected ICU admission, incidence of reintubation, and duration of hospitalizations

Sherman 2014 *(Continued)*

Notes	**Publication type:** meeting abstract **Country:** Israel **Conversions:** none **Authors' conclusions:** Use of sugammadex (compared with neostigmine) as a reversal agent following laparoscopic sleeve gastrectomy surgery was associated with higher postoperative oxygen saturation despite lower TOF count before administration of reversal agent. Lack of differences in other measured variables may stem from the small patient groups studied **Contact:** first trial author Tiberiu Ezri contacted by email: tezri@netvision.net.il on 26.05.2016; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized study"; no further information available
Allocation concealment (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of participants (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of personnel (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of primary outcome assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of safety assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to assess owing to insufficient information
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published meeting abstract clearly includes all expected outcomes
Funding bias	Unclear risk	Unable to assess owing to insufficient information
Other bias	Unclear risk	Unable to assess owing to insufficient information. Demographic data were similar between groups

Sustic 2012

Methods	**Study design:** prospective, randomized clinical study **Sample size calculation:** no information available
Participants	**Number of randomized participants:** 42

Sustic 2012 *(Continued)*

	Inclusion criteria: adults undergoing laparoscopic cholecystectomy **Exclusion criteria:** no information available
Interventions	**Anaesthesia:** no information available **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 0.15 to 3 mg/kg **Comparison:** sugammadex 2 mg/kg (n = 21) vs neostigmine 40 µg/kg + atropine group 15 µg/kg (n = 21) **Administration time of sugammadex or neostigmine:** no information available
Outcomes	Gastric emptying evaluated by paracetamol absorption test. Paracetamol absorption was assessed from the plasma paracetamol concentration (PPC)
Notes	**Publication type:** meeting abstract **Country:** Croatia **Conversions:** none **Authors' conclusions:** Although study results show a tendency toward faster gastric emptying in the sugammadex group, this difference is not significant in most, possibly owing to small sample size **Contact:** first author Alan Sustic contacted by email: alan.sustic@uniri.hr on 24.05.2016; replied 25.05 * Indicates unpublished data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomization *
Allocation concealment (selection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of participants (performance bias)	High risk	Participants not blinded *
Blinding of personnel (performance bias)	High risk	Participants not blinded *
Blinding of primary outcome assessment (detection bias)	Low risk	Not relevant as TOF measurement not performed in this study
Blinding of safety assessment (detection bias)	Low risk	Outcomes assessor was blinded *
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to assess owing to insufficient information
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published meeting abstract clearly includes all expected outcomes
Funding bias	Unclear risk	Unable to assess owing to insufficient information

Sustic 2012 *(Continued)*

Other bias	Unclear risk	Unable to assess owing to insufficient information

Tas 2015

Methods	**Study design:** randomized, prospective study **Sample size calculation:** performed, but no specific information available
Participants	**Number of randomized participants:** 52 **Inclusion criteria:** ASA I and II, age 18 to 65 years, scheduled for septoplasty operation **Exclusion criteria:** taking antiaggregant/anticoagulant treatment, history of bleeding disorder, abnormal complete blood count and coagulation tests (prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR))
Interventions	**Anaesthesia:** induced with propofol 2 to 2.5 mg/kg, fentanyl 0.5 µg/kg, maintained with sevoflurane 2%, remifentanil 0.25 µg/kg/min infusion **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: no information available **Comparison:** neostigmine 0.05 mg/kg + atropine 0.02 mg/kg (n = 26) vs sugammadex 2 mg/kg (n = 26) **Administration time of sugammadex or neostigmine:** reappearance of T2
Outcomes	Amount of bleeding measured by evaluating the blood leak on the nasal tip dressing over 3 hours postoperatively at 30 minute intervals during first hour, then every hour during the next 2 hours Blood samples were taken 120 minutes after administration of sugammadex or neostigmine for PT (seconds) and aPTT (seconds) measurements Mean arterial pressure (MAP; mmHg), mean heart rate (MHR; beats/min), peripheral oxygen saturation (SpO_2; %), and presence of nausea/vomiting (Likert scale) and pain (visual analogue scale)
Notes	**Publication type:** peer-reviewed article **Country:** Turkey **Conversions:** none **Authors' conclusions:** Sugammadex was associated with greater postoperative bleeding than neostigmine in patients undergoing septoplasty. For surgical procedures having high risk of bleeding, the safety of sugammadex needs to be verified **Contact:** first author Nilay Tas contacted by email: drnil.anest@hotmail.com on 26.05.2016; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization sequence was generated by using computer generated random numbers"
Allocation concealment (selection bias)	Low risk	"Randomization was performed using the previously prepared, sealed opaque envelopes"

Tas 2015 *(Continued)*

Blinding of participants (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of personnel (performance bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of primary outcome assessment (detection bias)	Unclear risk	Unable to assess owing to insufficient information
Blinding of safety assessment (detection bias)	Low risk	Measurements of quantity of bleeding done by the surgeon without knowledge of which drug was used
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants are accounted for, and missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups: 52 envelopes prepared for probable sample loss (26 for neostigmine, 26 for sugammadex). Two participants in Group S were discarded (1 participant did not come to surgery, and for another participant, surgery was postponed because of recent upper respiratory tract infection). So study population included 26 participants in the neostigmine group and 24 in the sugammadex group
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published article clearly includes all expected outcomes
Funding bias	Low risk	Source of support: departmental sources
Other bias	Unclear risk	No apparent other type of bias, except no information on sample size calculation. No differences between participant characteristics such as age, gender, surgery duration, and ASA classification

Woo 2013

Methods	**Study design:** randomized, parallel-group, active-controlled, safety assessor-blinded, phase 4 study **Sample size calculation:** powered to detect whether geometric mean recovery time to TOFR > 0.9 with sugammadex is ≥ 5 times faster than geometric mean time with neostigmine, and whether geometric mean recovery time to TOFR > 0.9 with sugammadex is < 3 minutes
Participants	**Number of randomized participants:** 128 **Inclusion criteria:** ASA I to III, either sex, aged > 18 years, of Korean descent, born in Korea, never having emigrated out of Korea and with a Korean home address, scheduled for elective surgery under general anaesthesia **Exclusion criteria:** any anatomical malformation that might cause difficult intubation; transferred to the ICU after surgery; neuromuscular disorders that could affect the NMB; significant renal or hepatic dysfunction; requirement of a pneumatic tourniquet during surgery; (family) history of malignant hyperthermia; allergy to opioids/opiates, cyclodextrins including sugammadex, muscle relaxants and their excipients, or other medications used during general anaesthesia; administration of toremifene and/or fusidic acid within 24 hours of study drug administration (or plan to administer these drugs within 24 hours after study drug administration); any condition contraindicating neostigmine and/or glycopyrrolate; pregnant females; participation in a previous sugammadex study; participation in another clinical drug study within 30 days inclusive of signing consent for the current study; or a member of, or related to, the investigational staff or sponsor staff

Woo 2013 *(Continued)*

Interventions	**Anaesthesia:** induced with intravenous propofol and maintained with inhalational sevoflurane. Opioids were administered according to local practice when clinically required **NMBA:** single intubation dose: rocuronium 0.6 mg/kg; maintenance dose: 0.1 to 0.2 mg/kg rocuronium as clinically required **Comparison:** sugammadex 2.0 mg/kg (n = 64) vs neostigmine 50 µg/kg plus glycopyrrolate 10 µg/kg (n = 64) **Administration time of sugammadex or neostigmine:** reappearance of T2
Outcomes	**Primary efficacy endpoint:** time from start of administration of sugammadex to recovery of TOFR to 0.9 **Secondary efficacy endpoints:** time to recovery of TOFR to 0.7 and 0.8; time to reappearance of T2 after last dose of rocuronium **Safety assessment:** adverse events, serious adverse events, vital signs, physical examination findings, clinical evidence of residual NMB and recurrence of NMB
Notes	**Publication type:** peer-reviewed article **Country:** 7 sites in the Republic of Korea **Conversions:** range to SD following guidelines from Hozo 2005 **Handling of adverse events:** No discrepancy exists between AEs presented in the original article and those reported in this review **Authors' conclusions:** Sugammadex was well tolerated and provided rapid reversal of moderate rocuronium-induced NMB in Korean patients, with recovery time 8.1 times faster than that of neostigmine. These results are consistent with those reported for Caucasian patients **Contact:** first trial author Tiffany Woo contacted first time by email: tiffany.woo@merck.com on 22.09.2015; has replied * Indicates unpublished data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible participants were randomized on a 1:1 basis A centralized computer-generated randomization schedule was used *
Allocation concealment (selection bias)	Low risk	Electronic interactive Web-based system, so randomization codes were located inside the system and could not be accessed until a participant was registered in the system and 1 code was assigned per participant *
Blinding of participants (performance bias)	Low risk	Participants were considered to be blinded, as they did not participate in the randomization procedure and were under general anaesthesia *
Blinding of personnel (performance bias)	High risk	The anaesthesiologist administering anaesthesia during the surgical procedure was not blinded to the randomized study drug, but was not allowed to reveal the assigned treatment group to the safety assessor
Blinding of primary outcome assessment (detection bias)	High risk	TOF-watch assessor was not blinded *

Woo 2013 *(Continued)*

Blinding of safety assessment (detection bias)	Low risk	Safety assessors were blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants are accounted for, and missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups: 128 participants randomized, all-subjects treated population: 120 (n = 60 in each group), intention to treat population: 118 (n = 59 in each group), per-protocol population: 116 (n = 59 in the sugammadex group, n = 57 in the neostigmine group). Two participants had major protocol violations (received neostigmine more than 2 minutes after reappearance of T2). All efficacy data for these participants were excluded from the per-protocol analysis set. Imputed data in both groups were due to loss of calibration of TOF watch during the course of the trial and inability to recalibrate the TOF watch to collect efficacy data *
Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrials.gov (NCT01050543), and all of the study's prespecified primary and secondary outcomes of interest to the review have been reported in the prespecified way
Funding bias	High risk	This study was sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA. Disclosures: Tiffany Woo and Phillip Phiri are employees of Merck Sharp & Dohme Corp., Whitehouse Station, NJ
Other bias	Low risk	Appears free of other sources of bias. Study sample size calculation designed to address this review's primary outcome. Participant demographics well balanced between treatment groups; types of elective surgical procedures performed are comparable

Wu 2014

Methods	**Study design:** randomized, parallel-group, multi-centre, safety assessor-blinded study **Sample size calculation:** powered to demonstrate that recovery of the TOFR to 0.9 after sugammadex 2 mg/kg is ≥ 2 times faster than after neostigmine 50 µg/kg
Participants	**Number of randomized participants:** Chinese 247, Caucasian 61, all in all 308 **Inclusion criteria:** age 18 to 64 years, ASA I to III, scheduled for elective surgery under general anaesthesia, allowing stable neuromuscular monitoring, which requires neuromuscular blockade using rocuronium; compliant with dose/visit schedules, and used an accepted method of contraception (if applicable). Chinese participants had to be born in China, to have never emigrated out of China, and to have a Chinese home address. Similarly, Caucasian participants had to be born in Europe, to have never emigrated out of Europe, and to have a European home address **Exclusion criteria:** anatomical malformations expected to lead to difficult tracheal intubation; neuromuscular disorders affecting NMB; significant renal/hepatic dysfunction (as determined by the investigator); (family) history of malignant hyperthermia; allergy to general anaesthesia medications; contraindication to study drugs; or clinically significant condition that may interfere with the trial (as determined by the investigator)
Interventions	**Anaesthesia:** Anaesthesia was induced and maintained with IV propofol according to clinical needs of the participant. Opioids could be administered according to local practice **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 0.1 to 0.2 mg/kg

Wu 2014 *(Continued)*

	Comparison: sugammadex 2 mg/kg (Chinese n = 126, Caucasian n = 29) vs neostigmine 50 µg/kg plus atropine 10 to 20 µg/kg (Chinese n = 121, Caucasian n = 32) **Administration time of sugammadex or neostigmine:** reappearance of T2
Outcomes	**Primary efficacy variable:** time from start of administration of sugammadex or neostigmine/atropine to recovery of TOFR to 0.9 **Secondary efficacy variable:** time to recovery of the TOFR to 0.7 and 0.8 **Safety assessments:** adverse events, serious adverse events, vital signs, and physical examination findings
Notes	**Publication type:** peer-reviewed article **Country:** 6 sites in China and 4 sites in Europe (2 sites in Denmark and 1 site each in Belgium and Norway) **Conversions:** Median + Range to Mean + SD following guidelines from Hozo 2005 **Handling of adverse events:** More detailed information regarding number of adverse events possibly, probably, or definitely related to study drug was provided by the authors through email correspondence, and we used these updated numbers in the review **Authors' conclusions:** Both Chinese and Caucasian participants recovered from NMB significantly faster after sugammadex 2 mg/kg than after neostigmine 50 µg/kg, with recovery that was ˜ 5.7 times (P < 0.0001) faster with sugammadex than with neostigmine in Chinese participants. Sugammadex was generally well tolerated **Contact:** first trial author Xinmin Wu contacted by email: xmwu2784@hotmail.com on 15.04.2016; no reply received; email sent to last author Woo 15.05.2016; replied 21.07.2016

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible participants were randomized via a central randomization system. Sponsor produced a computer-generated randomization schedule with treatment codes in blocks, using a validated SAS-based application. The schedule associated each treatment code with a participant number, and participants were randomized in a 1:1 ratio
Allocation concealment (selection bias)	Low risk	Central allocation (secondary to central randomization)
Blinding of participants (performance bias)	Low risk	Participants were blinded *
Blinding of personnel (performance bias)	High risk	Personnel in the OR were not blinded
Blinding of primary outcome assessment (detection bias)	High risk	TOF-watch assessor was not blinded
Blinding of safety assessment (detection bias)	Low risk	Safety assessments were performed by a safety assessor who was blinded to the treatment administered
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants are accounted for, and missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups: Of 247 randomized Chinese participants, 16 discontinued the

Wu 2014 *(Continued)*

		study, and one who completed the study had missing efficacy data. Hence, 231 Chinese participants received study treatment and were included in the safety analysis (AST group), and 230 Chinese subjects with evaluable data were included in the efficacy analysis (full analysis set; sugammadex n = 119, neostigmine n = 111). In total, 61 Caucasian participants were randomized, 60 of whom received treatment (AST group) and 59 who had evaluable data (full analysis set; sugammadex n = 29, neostigmine n = 30)
Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrials.gov (NCT00825812), and all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way
Funding bias	High risk	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA,. provided financial support to the study. Medical writing support was provided by Melanie More of Prime Medica Ltd., Knutsford, Cheshire, UK. This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA. HR is an employee of MSD, Oss, The Netherlands, and TW is an employee of Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA, both of whom may own stock and/or hold stock options in the Company. EA was formerly an employee of MSD, Oss, The Netherlands. XW, SY, JL, BV, LX, CC, VD, YY, HO, and YH work for institutions that received research funding from Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA. BV and VD have also received research funding from Merck & Co., Inc. for previous studies
Other bias	Low risk	Appears free of other sources of bias. Study sample size calculation designed to address this review's primary outcome. Baseline characteristics comparable within participant groups

Yagan 2015

Methods	**Study design:** single-blind, prospective, randomized, controlled study **Sample size calculation:** powered to detect 3 mmHg change in intraocular pressure
Participants	**Number of randomized participants:** 36 **Inclusion criteria:** ASA I to II, between 18 and 65 years of age, scheduled to have general anaesthesia with endotracheal intubation for elective surgery, written informed consent **Exclusion criteria:** undergoing laparoscopic surgery, ophthalmic surgery, predicted difficult tracheal intubation (Mallampati III/IV); history of glaucoma, uncontrolled hypertension, and cardiovascular disease; body mass index (BMI) > 30 kg/m^2; increased intracranial pressure; using drugs affecting IOP; surgical positions except supine position
Interventions	**Anaesthesia:** induced by fentanyl 1 µg/kg and propofol 2.5 mg/kg. Maintained with 2% sevoflurane in 50% O_2/air mixture and 0.2 to 0.7 µg/kg/min remifentanil infusion **NMBA:** single intubating dose: rocuronium 0.6 mg/kg; maintenance dose: rocuronium 0.1 to 0.2 mg/kg **Comparison:** sugammadex 2 mg/kg (n = 18) or neostigmine 0.05 mg/kg + atropine 0.02 mg/kg (n = 18) **Administration time of sugammadex or neostigmine:** TOF response T4/T1 at 20%
Outcomes	Heart rate (HR), mean arterial pressure (MAP), and intraocular pressure (IOP) were measured as baseline before the induction (T1), after application of reversal agent (T2), and at 1 (T3), 3 (T4), 5 (T5). and 10 (T6) minutes after extubation. Extubation time (time to TOFR of 90% after administration of reversal

Yagan 2015 *(Continued)*

	agent), amount of rocuronium and remifentanil consumption during surgery, and type and duration of surgery were recorded. Complications after surgery such as nausea, vomiting, and shivering
Notes	**Publication type:** peer-reviewed article **Country:** Turkey **Conversions:** Median + Range to Mean + SD following guidelines from Hozo 2005 **Handling of adverse events:** No discrepancy exists between AEs presented in the original article and those reported in this review **Authors' conclusions:** Lower end-extubation intraocular pressure levels were obtained when sugammadex was used as a neuromuscular block reversal agent in comparison with the neostigmine-atropine combination. Sugammadex may be a better option for reversal of neuromuscular blockade, and intraocular pressure increase should be avoided in patients with glaucoma or penetrating eye injury **Contact:** first trial author Ozgur Yagan contacted by email: ozguryagan@hotmail.com on 15.05.2016; replied 18.05.2016 * Indicates unpublished data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a computer-generated sequence of numbers and an opaque * sealed envelope technique, participants were randomly divided into 2 groups
Allocation concealment (selection bias)	Low risk	Using a computer-generated sequence of numbers and an opaque * sealed envelope technique, participants were randomly divided into 2 groups
Blinding of participants (performance bias)	High risk	Participants not blinded *
Blinding of personnel (performance bias)	High risk	Personnel not blinded *
Blinding of primary outcome assessment (detection bias)	High risk	TOF-watch assessor not blinded *
Blinding of safety assessment (detection bias)	Low risk	IOP measuring researcher and assessor of the quality of extubation were blinded *
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants are accounted for, and missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups: Of 49 patients approached, 13 had to be excluded (BMI > 30 kg/m^2 n = 6; uncontrolled hypertension n = 4; ASA III and above, n = 3) and 36 represented the final sample, which was randomly divided into 2 groups of 18 each
Selective reporting (reporting bias)	Low risk	Study protocol is available on clinicaltrials.gov (NCT02215382), and all of the study's prespecified outcomes of interest to the review have been reported in the prespecified way *
Funding bias	Low risk	Study funded by trial authors themselves *

Yagan 2015 *(Continued)*

Other bias	Low risk	Study sample size calculation designed to address this review's secondary outcome. No significant differences between groups regarding age, gender, BMI, and ASA scores

List of acronyms and abbreviations used in these tables

AE - adverse events; aPTT - activated partial thromboplastin time; ASA - American Society of Anesthesiologists; AST - aspartate aminotransferase; BIS - Bispectral index; BMI - body mass index; BP - blood pressure; BUN - blood urea nitrogen; C - clearance; CBW - corrected body weight; CNS - central nervous system; COPD - chronic obstructive pulmonary disease; Cr - creatinine; Cys - cysteine; ECG - electrocardiography; FOC - free of charge; FT_3 - free triiodothyronine; FT_4 - free thyroxine; Hg - haemoglobin; HR - heart rate; IBW - ideal body weight; ICU - intensive care unit; INR - international normalized ratio; IOP - intraocular pressure; ITT - intention to treat; IV - intravenous; LBS - Laparoscopic Bariatric Surgery; LBW - lean body weight; MAC - minimal alveolar concentration; MAP - mean arterial blood pressure; MBP - mean blood pressure; MG - myasthenia gravis; Mg - magnesium; MHR - mean heart rate; min - minimum; MMSE - Mini-Mental State Examination; MO - morbidly obese; NM - neuromuscular; NMB - neuromuscular blockade; NMBA - neuromuscular blocking agents; NMT - neuromuscular technique; NYHA - New York Heart Association; $PaCO_2$ - partial pressure of carbon dioxide; PACU - post-anaesthesia care unit; PONV - postoperative nausea and vomiting; PORC - postoperative residual curarization; PPC - plasma paracetamol concentration; PRSES - postoperative respiratory system evaluation score; PT - prothrombin time; PTC - post-tetanic count; QTc - QTc interval; RPONB - residual postoperative neuromuscular blockade; SAE - serious adverse event; SAS - SAS institute; SD - standard deviation; SEVO - sevoflurane; SO - super obese; SpO_2 - peripheral oxygen saturation; SRS - surgical rating scale; SX - symptoms; T2 - second twitch; TOF - train of four; TOFR - train-of-four ratio; TSH - thyroid-stimulating hormone; XLIF - extreme lateral interbody fusion

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aho 2012	Study outcomes not of interest to our review RCT investigating elevated BIS and entropy values after reversal with sugammadex 200 mg vs neostigmine 2.5 mg following rocuronium 0.6 mg kg^{-1}
Baysal 2013	Study outcomes not of interest to our review RCT investigating use of sugammadex 1 mg kg^{-1} for reversal of residual blockade after administration of neostigmine 0.07 mg kg^{-1} and atropine 0.02 mg kg^{-1}
Dahaba 2012	Study outcomes not of interest to our review RCT investigating effects of sugammadex 4 mg kg^{-1} vs neostigmine 0.05 mg kg^{-1}/glycopyrrolate 0.01 mg kg^{-1} neuromuscular block reversal on bispectral index monitoring
Gaona 2012	Study included 30 paediatric patients, aged 2 to 11 years RCT comparing efficacy and safety of reversal with sugammadex 4 mg kg^{-1} vs neostigmine 0.05 mg kg^{-1}/atropine 0.025 mg kg^{-1} in paediatric patients with deep blockade induced by rocuronium 0.6 mg kg^{-1}
Ghoneim 2015	RCT investigating use of sugammadex and neostigmine for reversing profound NMB in paediatric neurosurgical patients who have undergone posterior fossa tumour excision
Harazim 2014	Same meeting abstract data later published in peer-reviewed article (Stourac 2016)
Kakinuma 2013	Study comparison not relevant to our review. RCT comparing sugammadex 1 mg/kg vs sugammadex 0.5 mg/kg + neostigmine 0.04 mg/kg, examining the cost of reversal and recovery time

Study	Reason for exclusion
Kara 2014	RCT in paediatric population, comparing efficacy of sugammadex and neostigmine for reversing NMB in 80 paediatric patients, aged 2 to 12 years, undergoing outpatient surgical procedures
Kzlay 2013	Same meeting abstract data later published in peer-reviewed article (Kizilay 2016)
Nagashima 2016	Study outcomes not of interest to our review Effects of neostigmine and sugammadex on QT interval and QT dispersion Participants received a combination of neostigmine and atropine or sugammadex (2 mg/kg) for reversal of neuromuscular blockade
Nagy 2014	Study retracted owing to changes in protocol made by trial authors, after the protocol was submitted to the Ethics Comittee of the Department of Anesthesiology, Faculty of Medicine, Cairo University, Egypt
NCT03111121	Study outcomes not of interest to our review Trial examines use of sugammadex for reversal of paralysis in microlaryngoscopy
Nemes 2016	Not an RCT. Trial is a prospective, partially randomised, placebo-controlled, double-blind, four-group parallel-arm study. Participants received nothing (recover spontaneously), sugammadex, neostigmine, or placebo at the preference of each anaesthesiologist
Ozgun 2014	Study included paediatric patients and compared clinical effects of sugammadex vs combination of anticholinergic-anticholinesterase agents for reversing of non-depolarizing neuromuscular block
Pecek 2013	Prospective, observational study. Participants received sugammadex or neostigmine at the preference of each anaesthesiologist
Sacan 2007	Not a truly randomized process, as participants could choose to not be included in the sugammadex group
Schepens 2015	Study included healthy volunteers and compared electromyographic activity of the diaphragm (EMGdi) during recovery from neuromuscular blockade using neostigmine and sugammadex
Stourac 2016	Study comparison not relevant to our review RCT comparing muscle relaxation induced with rocuronium 1 mg/kg, reversal with sugammadex 2 to 4 mg/kg with succinylcholine 1 mg/kg for induction, rocuronium 0.3 mg/kg for maintenance, and neostigmine 0.03 mg/kg for reversal of neuromuscular blockade
Veiga Ruiz 2011	Study performed on 24 paediatric patients, aged 2 to 9 Aim of the RCT was to compare the efficacy and security of sugammadex 2 mg kg^{-1} vs neostigmine 0.05 mg kg^{-1}/atropine 0.025 mg kg^{-1} in reversing moderate blockade with rocuronium 0.45 mg kg^{-1}

List of acronyms and abbreviations used in these tables
BIS - Bispectral Index; EMGd - diaphragmatic electromyogram; NMB - neuromuscular blockade; RCT - randomized controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Kim 2016

Methods	**Allocation:** computer-generated randomization

Kim 2016 *(Continued)*

	Intervention model: parallel assignment **Masking:** state blinded, no additional details **Primary purpose:** treatment
Participants	**Enrolment:** 80 adult patients **Inclusion criteria:** • Age 20 to 64 years • Both sexes • American Society of Anesthesiologists physical status I to II • Received elective surgery under general anaesthesia with rocuronium for intubation and maintenance **Exclusion criteria:** • Predicted difficult intubation • Previous known neuromuscular disease that may affect neuromuscular blockade • Allergy to any drug used in general anaesthesia • History of serious liver or kidney disease • Use of drugs that might interact with neuromuscular muscular blocking agents • Pregnancy • Obesity (defined as body mass index (BMI) ≥ 30 kg/m^2)
Interventions	**Control group:** neostigmine 50 mg/kg with glycopyrrolate 10 mg/kg after operation **Intervention group:** sugammadex 2.0 mg/kg after operation
Outcomes	Primary objective was to determine recovery time and response after sugammadex or neostigmine administration of first twitch (T1) and train-of-four ratio (TOFR) to 0.9 during rocuronium-induced moderate neuromuscular blockade
Notes	This study has been completed. Data will be published in the next updated version of this review

NCT02243943

Methods	**Allocation:** randomized **Intervention model:** parallel assignment **Masking:** double-blind (participant, investigator) **Primary purpose:** treatment
Participants	Enrolment: 100 **Inclusion criteria:** • Age 18 years • Body mass index (BMI) < 35 • American Society of Anesthesiologists (ASA) class I to III • Scheduled for surgery requiring general anaesthesia with a neuromuscular blocking agent • Ability to give oral and written informed consent **Exclusion criteria:**

NCT02243943 *(Continued)*

	• Failure to meet inclusion criteria - known or suspected neuromuscular disorders impairing neuromuscular function; allergy to muscle relaxants, anaesthetics, or narcotics • (Family) history of malignant hyperthermia; women who are or may be pregnant or are currently breastfeeding; contraindications for use of neostigmine; intestinal obstruction, chronic obstructive pulmonary disease (COPD), Global Initiative for Obstrutive Lung Disease (GOLD) 4; abnormal heart rhythm (e.g. bradycardia: < 40/min); surgery requiring neuraxial anaesthesia/analgesia; preoperative cognitive dysfunction or mental disabilities; preexistent significant pulmonary disease with preoperative peripheral oxygen saturation (SpO_2) < 90%; preoperative intensive care unit (ICU) treatment/intubation (ICU patient);need for postoperative ICU treatment or ventilation
Interventions	Sugammadex 2 to 4 mg/kg Neostigmine 1.0 to 2.5 mg and atropine 0.5 to 1.0 mg
Outcomes	**Primary outcome measures:** • Mean lowest saturation [Time frame: 45 minutes] [Designated as safety issue: no] Mean saturation is the mean value of beat-to-beat Hb-oxygen saturation measured by finger pulse oximeter, as measured in the first 45 minutes in the recovery room following surgery **Secondary outcome measures:** • Pain [Time Frame: 45 minutes] [Designated as safety issue: no] Using the 1 to 10 numerical rating scale • Sedation [Time Frame: 45 minutes] [Designated as safety issue: no] Using Leiden observer alertness score
Notes	This study has been completed. Based on personal correspondence with the last trial author, we became aware of preliminary results, published as a letter (September 2016), after our last search (2 May 2016). These data will be published in the next updated version of this review

Sen 2016

Methods	**Allocation:** randomized **Intervention model:** parallel assignment **Masking:** double-blind (participant, investigator) **Primary purpose:** safety/efficacy study
Participants	72 patients with American Society of Anesthesiologists (ASA) physical status I or II, scheduled for total thyroid surgery **Inclusion criteria:** 1. ASA physical status I or II 2. Age between 30 and 70 years **Exclusion criteria:** 1. Younger than 30 years 2. Older than 70 years 3. ASA score > 2 4. History of diabetes mellitus, peripheral arterial disease, gastrointestinal disease (diarrhoea, chronic constipation, gastritis, ulcers, irritable bowel disease, ulcerative colitis, Crohn's disease), laxative use, history of ileus or stroke 5. Abnormal levels of serum electrolyte or thyroid hormones

Sen 2016 *(Continued)*

Interventions	When 4 twitches were observed on train-of-four stimulation, neuromuscular block was reversed conservatively in the control group (neostigmine 0.04 mg/kg + atropine 0.015 mg/kg) and with sugammadex (sugammadex 2 mg/kg) in the study group
Outcomes	**Primary outcome measures:** Median time of first flatus **Secondary outcome measures:** Occurrences of nausea, vomiting, diarrhoea, or constipation.
Notes	This study has been completed. These data will be published in the next updated version of this review

Characteristics of ongoing studies *[ordered by study ID]*

NCT01539044

Trial name or title	Optimal relaxation technique for laparotomies with rocuronium infusion followed by sugammadex reversal (ProjectO5Rs)
Methods	**Allocation:** randomized **Endpoint classification:** safety/efficacy study **Intervention model:** parallel assignment **Masking:** double-blind (participant, caregiver, outcomes assessor) **Primary purpose:** treatment
Participants	**Enrollment:** 49 **Inclusion criteria:** • Age 18 to 75 years, ASA I to III • Elective or semi-emergency laparotomy under general anaesthesia needed tracheal intubation and muscle relaxation **Exclusion criteria:** • Severe renal impairment (CrCL < 30 mL/min) • Severe hepatic impairment • BMI > 30 kg m^2 • Known or suspected neuromuscular disorders • Allergy to narcotics, muscle relaxants, benzodiazepine, or other medication used during general anaesthesia • Hypersensitivity to active substance or to any of the excipients • Difficult intubation anticipated during physical examination • Contraindication to epidural analgesia • Aminoglycoside antibiotics, anticonvulsants, or magnesium, as these will interfere with the action of rocuronium • Pregnant, breastfeeding, or woman of child-bearing potential who is not using adequate contraception • Poor GCS and mental derangement, unable to give consent
Interventions	Active comparator: IB-neostigmine

NCT01539044 *(Continued)*

	Participant will be given intermittent bolus of rocuronium during surgery and reversal of neostigmine at completion of surgery at TOFR 2 Experimental: CI-sugammadex Participant will be given continuous infusion of rocuronium and reversal of sugammadex at completion of surgery at PTC 1 to 2
Outcomes	**Primary outcome measures:** • Speed of reversal [Time Frame: participant monitored until return of full muscle power, usually within 30 minutes] [Designated as safety issue: no]. Time from start of administration of reversal agent to recovery of T4/T1 ratio to 0.9 **Secondary outcome measures:** • Vital signs, i.e. heart rate and blood pressure [Time Frame: first 24 hours of postop period] [Designated as safety issue: yes] Pre-reversal, post-reversal, recovery, and post-anaesthetic visit • intraoperative events [Time Frame: throughout the operation, on average 3 hours] [Designated as safety issue: no] Events suggestive of inadequate paralysis during surgery, a composite incidence of movement, coughing, bucking, breathing against ventilator or surgeon complaining of tight abdomen • incidence of residual neuromuscular blockade [Time Frame: 1 hour] [Designated as safety issue: no] Composite occurrence of clinical signs of residual muscle weakness like diplopia, ptosis, non-sustained head-lift, T4/T1 ratio < 90%
Starting date	February 2012
Contact information	Principal investigator: Dr. Maria HS lee, MMed(Anaes), Clinical Research Centre, Johor, Malaysia
Notes	This study has been completed. No study data have been published to the best of our knowledge

NCT01748643

Trial name or title	CURES: The effect of deep curarization and reversal with sugammadex on surgical conditions and perioperative morbidity (CURES)
Methods	**Allocation:** randomized **Endpoint classification:** safety/efficacy study **Intervention model:** parallel assignment **Masking:** double-blind (participant, investigator, outcomes assessor) **Primary purpose:** supportive care
Participants	**Enrolment:** 60 **Inclusion criteria:** 1. Ability to give written informed consent 2. American Society of Anaesthesiologists class I, II, or III 3. Obese or morbid obese, as defined by BMI > 30 and > 40 kg/m^2, respectively **Exclusion criteria:** 1. Neuromuscular disorders

NCT01748643 *(Continued)*

2. Allergy to, or contraindication for, muscle relaxants, neuromuscular reversing agents, anaesthetics, narcotics
3. Malignant hyperthermia
4. Pregnancy or lactation
5. Renal insufficiency defined as serum creatinine 2× the upper normal limit, glomerular filtration rate < 60 mL/min, urine output < 0.5 mL/kg/h for at least 6 hours
6. Chronic obstructive pulmonary disease GOLD classification ≥ 2
7. Clinical, radiographic, or laboratory findings suggesting upper or lower airway infection
8. Congestive heart failure
9. Pickwick syndrome
10. Psychiatric illness inhibiting co-operation with study protocol or possibly obscuring results

Interventions

Drug: deep neuromuscular blockade with rocuronium, reversal with sugammadex

after induction of anaesthesia, a rocuronium infusion (0.6 mg/kg (lean body mass)/h) is started and titrated to a post-tetanic count of 1 to 2 twitches. At completion of surgery, neuromuscular blockade will be reversed with sugammadex 4 mg/kg. Participants are extubated when TOFR > 0.9

Drug: normal neuromuscular blockade reversal with rocuronium, reversal with neostigmine

After induction of anaesthesia, top-ups of rocuronium (10 mg) are given as needed to maintain a TOF count of 1 to 2. At completion of surgery, neuromuscular blockade will be reversed with neostigmine 50 µg/kg and glycopyrrolate 10 µg/kg (lean body mass). Patients are extubated when TOFR > 0.9

Outcomes

Primary outcome measures:

- Subjective evaluation of the view on the operating field by the surgeon [Time Frame: Participants will be followed for the duration of the laparoscopic gastric bypass surgery, an expected average of 1.5 hours] [Designated as safety issue: no] At completion of surgery, the view on the operating field will be graded by the surgeon using a 5-point rating scale
- Number of intra-abdominal pressure rises > 15 cmH_2O [Time Frame: Participants will be followed for the duration of the laparoscopic gastric bypass surgery, an expected average of 1.5 hours] [Designated as safety issue: no] Intra-abdominal pressure rises > 15 cmH_2O as detected by the intra-abdominal CO_2 insufflator

Secondary outcome measures:

- Respiratory function [Time Frame: measured the day before surgery and 30 minutes after completion of surgery (when the modified observer's assessment of alertness/sedation scale is 5 (participant responds readily to name spoken in normal tone))] [Designated as safety issue: yes] Respiratory function will be assessed by measuring peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV_1) with the Vitalograph electronic portable peak flow meter. A mean of 3 measurements will be taken in upright posture in bed before and after surgery
- Oxygen saturation [Time Frame: measured the day before surgery and 30 minutes after completion of surgery (when the modified observer's assessment of alertness/sedation scale is 5 (participant responds readily to name spoken in normal tone))] [Designated as safety issue: yes] Oxygen saturation will be measured non-invasively with a pulse oximeter
- Effect of pneumoperitoneum on cerebral tissue oxygenation [Time Frame: Participants will be followed for an expected average of 5 minutes after the start of intra-abdominal CO_2 insufflation by the surgeon] [Designated as safety issue: no] Using near-infrared spectroscopy (Fore-sight) technology, absolute brain tissue oxygenation can be quantified non-invasively by applying 2 skin electrodes to the forehead of the patient
- Effect of neuromuscular blockade on cerebral tissue oxygenation [Time Frame: Participants will be followed for an expected average of 5 minutes after intravenous injection of rocuronium] [Designated as safety issue: no] Using near-infrared spectroscopy (Fore-sight) technology, absolute brain tissue oxygenation can be quantified non-invasively by applying 2 skin electrodes to the forehead of the patient

NCT01748643 *(Continued)*

	• Effect of reversal of neuromuscular blockade (with sugammadex or neostigmine) on cerebral tissue oxygenation [Time Frame: Participants will be followed for an expected average of 5 minutes after intravenous injection of sugammadex or neostigmine] [Designated as safety issue: no] Using near-infrared spectroscopy (Fore-sight) technology, absolute brain tissue oxygenation can be quantified non-invasively by applying 2 skin electrodes to the forehead of the patient
Starting date	April 2013
Contact information	Pascal Vanelderen, MD, Principal Investigator, Ziekenhuis Oost-Limburg
Notes	This study has been completed. No data have yet been published to the best of our knowledge

NCT02160223

Trial name or title	Sugammadex compared with neostigmine/atropine for neuromuscular block reversal in patients with obstructive sleep apnoea
Methods	**Allocation:** randomized **Endpoint classification:** efficacy study **Intervention model:** parallel assignment **Masking:** double-blind (participant, outcomes assessor) **Primary purpose:** treatment
Participants	**Inclusion criteria:** ASA I to III scheduled for surgery for obstructive sleep apnoea **Exclusion criteria:** Neuromuscular disorders, hepatic or renal dysfunction, allergy to study drugs, using medication that could interfere with NMBAs, pregnancy or breastfeeding
Interventions	Group S participants will receive 2 mg kg^{-1} sugammadex at completion of surgery Group N participants will receive 50 µg kg^{-1} neostigmine and 0.5 mg atropine at completion of surgery
Outcomes	**Primary outcome measures:** • TOFR = 0.9 time [Time Frame: postoperative 5 minutes] [Designated as safety issue: no] TOFR = 0.9 time will be recorded from the TOF-watch after study drug administration **Secondary outcome measures:** • Desaturation [Time Frame: postoperative 5 minutes] [Designated as safety issue: yes] Participants will be monitored for desaturation after extubation • Bradycardia [Time Frame: postoperative 5 minutes] [Designated as safety issue: no] Heart rate will be monitored after extubation • Tachycardia [Time Frame: postoperative 5 minutes] [Designated as safety issue: no] Heart rate will be monitored after extubation **Other outcome measures:** • Operation room time [Time Frame: postoperative 30 minutes] [Designated as safety issue: no] Time elapsed from study drug administration to time the participant was transferred to the PACU

NCT02160223 *(Continued)*

	• PACU time [Time Frame: postoperative 1 hour] [Designated as safety issue: no] Time elapsed from time participant entered the PACU to time participant left the PACU
Starting date	January 2012
Contact information	Principal Investigator: Dilek Yazicioglu, Dişkapı Yildirim Beyazit Teaching and Research Hospital
Notes	This study has been completed. No study results have been published yet to the best of our knowledge

NCT02256280

Trial name or title	A randomized double blind controlled trial comparing sugammadex and neostigmine after thoracic anaesthesia (DATA)
Methods	**Allocation:** randomized **Endpoint classification:** safety/efficacy study **Intervention model:** parallel assignment **Masking:** double-blind (participant, caregiver, investigator)
Participants	**Estimated enrolment:** 266 **Inclusion criteria:** • Scheduled for pulmonary resection, lobectomy, pneumonectomy, bullectomy, pleurodesis • Age 18 to 70 years • ASA class I, II, III • BMI = 18 to 30 kg/m^2 **Exclusion criteria:** • Scheduled for oesophagectomy, thoracotomy, vascular resection • COPD GOLD class III or IV, respiratory infection, asthma • Preoperative FEV_1 < 60% of predicted, FEV_1/forced vital capacity ratio (FEV_1/FVC) < 70% • Preoperative diffusion lung capacity for carbon monoxide/alveolar volume ratio (DLCO/VA) < 60% of predicted • Preoperative oxygen saturation (SpO_2) < 92% or partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO_2/FiO_2) ratio < 300 • Cardiovascular disease with metabolic equivalent of tasks (METS) score < 4 • Neuromuscular disorder • Kidney failure defined as estimated glomerular filtration rate (eGFR) < 30 mL/min/1,73 m^2 • Pregnant women
Interventions	Sugammadex 2 or 4 mg/kg IV once at completion of surgery Neostigmine 0.05 or 0.07 mg/kg (+ atropine 0.02 mg/kg) IV once at completion of surgery
Outcomes	**Primary outcome measures:** • Mean time from reversal administration to TOFR = 0.9 [Time Frame: at the end of general anaesthesia] [Designated as safety issue: no] Time from reversal administration to at least 3 TOFR ≥ 0.9 **Secondary outcome measures:**

NCT02256280 *(Continued)*

- Mean time from reversal administration to TOFR = 1.0 [Time Frame: at the end of general anaesthesia] [Designated as safety issue: no] Time from reversal administration to at least 3 TOFR value ≥ 1.0
- Mean time from reversal administration to extubation [Time Frame: at the end of anaesthesia] [Designated as safety issue: no] Time from reversal administration to tracheal extubation
- Muscular weakness incidence [Time Frame: in the first 60 minutes after extubation] [Designated as safety issue: yes] Measured by tongue depressor test
- Hypoxaemia or hypercapnia incidence [Time Frame: in the first 60 minutes after extubation] [Designated as safety issue: yes] Hypoxaemia defined as partial pressure of oxygen in arterial blood/Fraction of inspired oxygen ratio (PaO_2/FiO_2) < 300. Hypercapnia defined as partial pressure of carbon dioxide in arterial blood ($PaCO_2$) > 45 mmHg
- Adverse events incidence [Time Frame: in the first 60 minutes after extubation] [Designated as safety issue: yes] Incidence of nausea or vomiting, abdominal pain, cardiac arrhythmias, hypotension coded according to Medical Dictionary for Regulatory Activities (MedDRA) terminology
- Postoperative complications incidence [Time Frame: Participants will be followed for the duration of hospital stay, an expected average of 7 days] [Designated as safety issue: yes] Incidence of medical and surgical complications coded according to MedDRA terminology

Other outcome measures:

- Mean time of hospital discharge [Time Frame: Participants will be followed for the duration of hospital stay, an expected average of 7 days] [Designated as safety issue: no] Time from intervention date to hospital discharge
- Postoperative complications incidence [Time Frame: at 30 days after surgery] [Designated as safety issue: yes] Incidence of medical and surgical complications coded according to MedDRA terminology

Starting date	January 2015
Contact information	Contact: Federico Piccioni, MD, +39223902282: federico.piccioni@istitutotumori.mi.it Fondazione IRCCS Istituto Nazionale dei Tumori, Milano
Notes	This study is currently recruiting participants. Estimated Study Completion Date: July 2017

NCT02330172

Trial name or title	Sugammadex provides better surgical condition compared with neostigmine in laryngeal microsurgery
Methods	**Allocation:** randomized **Endpoint classification:** efficacy study **Intervention model:** parallel assignment **Masking:** single-blind (outcomes assessor) **Primary purpose:** treatment
Participants	**Estimated enrolment:** 80 **Inclusion criteria:** • ASA physical status classification I or II elective laryngeal microsurgery under general anaesthesia **Exclusion criteria:**

NCT02330172 *(Continued)*

	• BMI > 25 or < 20 kg/m^2; taking intercurrent medication glutamic oxaloacetate transaminase or glutamic pyruvate transaminase > 40 IU/L, Cr > 1.4 mg/dL
Interventions	**Active comparator:** rocuronium 0.45 - neostigmine when anaesthetic induction in rocuronium 0.45 mg/kg will be administered for muscle relaxation At completion of operation, injection of neostigmine or sugammadex will be administered **Active comparator:** rocuronium 0.9 - sugammadex When anaesthetic induction, rocuronium 0.9 mg/kg will be injected to rocuronium 0.9 - sugammadex group for muscle relaxation At completion of operation, an injection of neostigmine or sugammadex will be administered
Outcomes	**Primary outcome measures:** • Satisfaction score of surgical condition [Time Frame: intraoperative surgical condition] [Designated as safety issue: no] Satisfaction score of surgical condition using 7 point Likert scale **Secondary outcome measures:** • Recovery time from neuromuscular blockade [Time Frame: from injection of neostigmine or sugammadex up to 30 minutes] [Designated as safety issue: no]
Starting date	December 2014
Contact information	Principal Investigator: Ah Young Oh, Seoul National University Hospital
Notes	Study completion date: August 2016. This study has been completed. No study results have been published yet to the best of our knowledge

NCT02361060

Trial name or title	Effects of neuromuscular block reversal with sugammadex vs neostigmine on postoperative respiratory outcomes after major abdominal surgery
Methods	**Allocation:** randomized **Endpoint classification:** safety/efficacy study **Intervention model:** parallel assignment **Masking:** open-label **Primary purpose:** treatment
Participants	**Estimated enrolment:** 130 **Inclusion criteria:** • Every patient scheduled for major abdominal surgery (liver resection, pancreatectomy, gastrectomy, or any type of colectomy) will be nominated to participate in the study • Informed consent will be asked for after admission to hospital the day before surgery • Postoperative epidural analgesia **Exclusion criteria:** • Refusal to participate

NCT02361060 *(Continued)*

	• Entry to postoperative recovery unit under mechanical ventilation • Hypersensitivity reactions to any study drugs • Severe asthma and mild asthma under treatment • Myocardial infarction or coronary occlusion 3 months before surgery • Myasthenia gravis • Emergency surgery • Pulmonary fibrosis or very severe chronic obstructive lung disease (GOLD IV)
Interventions	Sugammadex 4 mg/kg Neostigmine 40 µg/kg in combination with atropine 10 µg/kg.
Outcomes	**Primary outcome measures:** • Change from baseline in FVC at 1 hour after surgery [Time Frame: basal and 1 hour after surgery] [Designated as safety issue: no] **Secondary outcome measures:** • Atelectasis size determined by lung ultrasound (planimetry) [Time Frame: 1 hour after surgery] [Designated as safety issue: no] • Atelectasis size determined by lung ultrasound (planimetry) [Time Frame: 24 hours after surgery] [Designated as safety issue: no] • $pO_2/FiO_2 < 300$ [Time Frame: 1 hour after surgery] [Designated as safety issue: no] • Association between atelectasis size and FVC [Time Frame: 1 hour after surgery] [Designated as safety issue: no] Atelectasis size (sq cm) will me measured by planimetry • Association between atelectasis size and FVC [Time Frame: 24 hours after surgery] [Designated as safety issue: no] Atelectasis size (sq cm) will me measured by planimetry • Association between atelectasis size and pO_2/FiO_2 [Time Frame: 1 hour after surgery] [Designated as safety issue: no] Atelectasis size (sq cm) will me measured by planimetry • Association between atelectasis size and pO_2/FiO_2 [Time Frame: 24 hours after surgery] [Designated as safety issue: no] Atelectasis size (sq cm) will me measured by planimetry
Starting date	February 2015
Contact information	Anesthesiology Service. Hospital Universitario La Princesa Enrique EAM Alday, MD +34 91 5202476; kikealday@hotmail.com Principal Investigator: Enrique EAM Alday, MD Sub-Investigator: Antonio APR Planas, MD Sub-Investigator: Manuel MMM Muñoz, MD Sub-Investigator: Esperanza EML Mata, MD Sub-Investigator: Carlos CAZ Álvarez, MD
Notes	This study is currently recruiting participants. Estimated Study Completion Date: December 2016

NCT02414880

Trial name or title	Sugammadex versus neostigmine in patients with liver cirrhosis undergoing liver resection
Methods	**Allocation:** randomized

NCT02414880 *(Continued)*

	Endpoint classification: pharmacodynamics study **Intervention model:** parallel assignment **Masking:** open-label **Primary purpose:** treatment
Participants	**Estimated enrolment:** 60 **Inclusion criteria:** • ASA class I for patients with preoperative normal liver function test (2 groups) and I to III for those with liver cirrhosis (2 groups). • For the 2 "Liver cirrhosis" groups: patients with liver cirrhosis with Child classification "A" and a Model for End-Stage Liver Disease (MELD) score < 10 undergoing liver resection surgery • For the 2 "Normal liver" groups: patients with normal preoperative liver function undergoing liver resection surgery **Exclusion criteria:** • Coexisting neuromuscular disease • BMI > 35 kg/m^2 • Renal impairment • Medications known to affect neuromuscular transmission (e.g. aminoglycoside antibiotics, magnesium sulphate) • Bleeding tendency • Intraoperative adverse events (e.g. massive bleeding, hypothermia)
Interventions	Sugammadex 2 mg/kg - normal liver Neostigmine 50 micrograms/kg combined with atropine 20 micrograms/kg - normal liver Sugammadex 2 mg/kg - liver cirrhosis Neostigmine 50 micro-grams/kg combined with atropine 20 micro-grams/kg - liver cirrhosis
Outcomes	**Primary outcome measures:** • Time from reversal to TOFR = 0.9 [Time Frame: 15 minutes] [Designated as safety issue: no] Time from administration of sugammadex or neostigmine to recovery of TOFR to 0.9 **Secondary outcome measures:** • Time from reversal to TOFR = 1 [Time Frame: 30 minutes] [Designated as safety issue: no] Time from administration of sugammadex or neostigmine until recovery of TOFR = 1 • Length of stay in the post-anaesthesia care unit (PACU) [Time Frame: 4 hours] [Designated as safety issue: no] Time required in post-anaesthesia care unit (PACU) to achieve a modified Aldrete score of 9 • Time from last rocuronium dose to TOFR = 0.9 [Time Frame: 1 hour] [Designated as safety issue: no] Time from last dose of rocuronium to recovery of TOFR = 0.9 • Duration of action of initial intubating dose of rocuronium [Time Frame: 45 minutes] [Designated as safety issue: no] Time interval between initial rocuronium intubating dose administration and recovery of first twitch of TOF response (T1) • Incidence of postoperative recurarization [Time Frame: 4 hours] [Designated as safety issue: yes] Recurrence of neuromuscular block (recurarization) will be defined as a decrease in TOFR to < 0.9 after full recovery had been detected, or as deterioration in clinical signs of recovery from the block • Total dose of rocuronium [Time Frame: 24 hours] [Designated as safety issue: no] Total dose of rocuronium used during the whole operation including intubating dose and subsequent top-ups

NCT02414880 *(Continued)*	
	• Duration of anaesthesia [Time Frame: 24 hours] [Designated as safety issue: no] Duration between induction of anaesthesia and complete recovery of consciousness and motor power
Starting date	December 2014
Contact information	Mohamed Abdulatif Mohamed, MD, Cairo University
Notes	This study has been completed. No study results have been published yet to the best of our knowledge

NCT02454504	
Trial name or title	Quality of awakening and impact on cognitive function after administration of sugammadex in robotic radical cystectomy
Methods	**Allocation:** randomized **Intervention model:** parallel assignment **Masking:** open-label
Participants	**Estimated enrolment:** 60 **Inclusion criteria:** • ASA score ≤ III • Underwent robotic cystectomy **Exclusion criteria:** • Cerebrovascular disease • BMI ≥ 30
Interventions	Sugammadex at completion of surgery Neostigmine at completion of surgery
Outcomes	**Primary outcome measures:** • Average score obtained on awakening according to specific test [Time Frame: 16 months] [Designated as safety issue: yes] Cognitive function as assessed by the Mini-Mental State Exam; quality of awakening as assessed by the Observer's Assessment of Alertness/Sedation
Starting date	March 2014
Contact information	Ester Forastiere, Dr, 0039 06 52662995: forastiere@ifo.it Regina Elena Cancer Institute Rome, RM, Italy, 00144 Sub-Investigator: Claudia Claroni, MD
Notes	This study is currently recruiting participants. Estimated Primary Completion Date: December 2016

NCT02648503

Trial name or title	Deep neuromuscular block and sugammadex versus standard of care on quality of recovery in patient undergoing elective laparoscopic cholecystectomy
Methods	**Allocation:** randomized **Endpoint classification:** efficacy study **Intervention model:** parallel assignment **Masking:** single-blind (outcomes assessor) **Primary purpose:** treatment
Participants	**Estimated enrolment:** 120 **Inclusion criteria:** • All adult patients (> 18 years) scheduled for elective laparoscopic cholecystectomy with ASA class I to III in Hospital of University of Medicine and Pharmacy-Ho Chi Minh City **Exclusion criteria:** • ASA class IV • Age < 18 years • Inability to sign informed consent • History or suspicion of neuromuscular disorder • Allergy to rocuronium or sugammadex, anaesthetics, or narcotics • History of malignant hyperthermia • Contraindication with neostigmine administration • Pregnancy or breastfeeding • Renal and liver insufficiency
Interventions	Deep neuromuscular block using rocuronium and reversal with sugammadex Moderate neuromuscular block using rocuronium and reversal with neostigmine (1 to 2 mg) and atropine (0.5 to 1 mg)
Outcomes	**Primary outcome measures:** • Quality of recovery [Time Frame: 40 minutes (T40) after completion of surgery] [Designated as safety issue: no] Primary outcome is to assess differences in quality of recovery or overall recovery on the post-operative quality recovery scale (PQRS) instrument at 40 minutes (T40) after completion of surgery between deep NMB (reversed with sugammadex) and standard of care in patients who undergo laparoscopic cholecystectomy. PQRS includes 6 domains of recovery: physiological, nociceptive, emotive, activities of daily living, cognitive, and overall patient perspective. Each domain comprises a series of questions. The PQRS will be completed and recorded face-to-face by anaesthesiologists in hospital and by telephone after discharge. The PQRS is completed before surgery to provide baseline values. Recovery is defined as returning to baseline values or better for each of the questions or assessments **Secondary outcome measures:** • Quality of recovery [Time Frame: 15 minutes (T15), and first day and 3 days after completion of surgery] [Designated as safety issue: no] Differences in quality of recovery or overall recovery of the PQRS instrument at 15 minutes (T15), and first day and 3 days after completion of surgery- Differences between each domain of PQRS instrument from 2 groups • Shoulder tip pain [Time Frame: first hour, 6 hours and 24 hours after surgery] [Designated as safety issue: no] Using a 100 mm visual analogue scale (VAS) (0 indicating no pain and 100 worst imaginable pain) **Other outcome measures:**

NCT02648503 *(Continued)*

- Surgical condition [Time Frame: intraoperation] [Designated as safety issue: no] Satisfaction of surgeon with surgical condition from deep neuromuscular block against moderate neuromuscular block. Surgeons will rate the surgical condition using a 5-point surgical condition scale (SRS) ranging from 1 = poor condition to 5 = optimal surgical condition after surgery
- Time to discharge readiness [Time Frame: every 20 minutes from start of admission to post-anaesthesia care unit (PACU), up to 2 hours] [Designated as safety issue: no] Time to discharge readiness from post-anaesthesia care unit (PACU) using post anaesthesia discharge score system (PADSS)
- Duration of operation [Time Frame: intraoperation] [Designated as safety issue: no] Duration of surgery: from successful abdominal access with trocars to skin closure duration from reversal to extubation (TOFR > 0.9)

Starting date	March 2016
Contact information	Vu TN Phan, PhD. MD +84-908883458: vuphan682003@yahoo.com Ho Chi Minh City University of Medicine and Pharmacy
Notes	This study is not yet open for participant recruitment

NCT02666014

Trial name or title	Sugammadex versus neostigmine for postoperative nausea and vomiting after laparoscopic gynaecological surgery
Methods	**Allocation:** randomized **Endpoint classification:** efficacy study **Intervention model:** parallel assignment **Masking:** double-blind (participant, investigator) **Primary purpose:** prevention
Participants	**Estimated enrolment:** 300 **Inclusion criteria:** 1. Female 2. In-patient 3. Age ≥ 21 years 4. ASA class 1 or 2 5. Undergoing elective laparoscopic, abdominal, gynaecological surgery. 6. Weight ≥ 40 kg or ≤ 100 kg 7. ≥ 3 risk factors for nausea and vomiting 8. Ability to give valid, informed consent 9. Duration of surgery expected to be ≥ 120 minutes. **Exclusion criteria:** 1. < 3 risk factors for PONV 2. Nausea and/or vomiting in past 72 hours before surgery 3. Regular antiemetic or opioid use 4. Obesity, with body weight ≥ 100.1 kg 5. History of drug or alcohol abuse 6. ASA III or worse

NCT02666014 *(Continued)*

	7. Laparoscopic surgery that is converted to open surgery 8. Age ≤ 20 years 9. Unknown pregnancy status in premenopausal women or those currently pregnant or breastfeeding. 10. Smoker 11. Anaphylaxis or hypersensitivity to study drug(s) 12. Day surgery procedure, unsuitable for follow-up at 6 hours and 24 hours postoperatively
Interventions	Sugammadex 2 mg/kg, to be given as a single dose via intravenous injection upon completion of surgery and guided by peripheral nerve stimulation Neostigmine 0.040 mg/kg, along with atropine 0.015 mg/kg, diluted in normal saline to make up 5 mL total volume to maintain blinding
Outcomes	**Primary outcome measures:** • Incidence of self-reported PONV at 6 hours after neuromuscular blockade reversal with sugammadex or neostigmine, in women at high risk of PONV, after undergoing laparoscopic gynaecological surgery [Time Frame: 6 hours after surgery] [Designated as safety issue: no] **Secondary outcome measures:** • Incidence of self-reported PONV following administration of sugammadex or neostigmine reversal for neuromuscular blockade 24 hours following laparoscopic gynaecological surgery in women at high risk of PONV [Time Frame: 24 hours after surgery] [Designated as safety issue: no] • Severity of self-reported PONV after administration of sugammadex or neostigmine for neuromuscular blockade reversal at 6 hours and 24 hours after undergoing laparoscopic gynaecological surgery in women at high risk of PONV [Time Frame: 6 and 24 hours after surgery] [Designated as safety issue: no] • Time interval from administration of sugammadex or neostigmine to administration of the first antiemetic dose in women at high risk of PONV following laparoscopic gynaecological surgery [Time Frame: up to 24 hours after surgery] [Designated as safety issue: no] • Pain intensity after administration of sugammadex or neostigmine for neuromuscular blockade reversal in women at high risk for PONV at 6 hours and 24 hours following laparoscopic gynaecological surgery [Time Frame: 6 hours and 24 hours after surgery] [Designated as safety issue: no] • Quality of recovery score after administration of sugammadex or neostigmine for neuromuscular blockade reversal in women at high risk of PONV at 24 hours following laparoscopic gynaecological surgery [Time Frame: 24 hours after surgery] [Designated as safety issue: no]
Starting date	June 2015
Contact information	KK Women's and Children's Hospital, Singapore, Jing Wen Ng: Ng.Jing.Wen@kkh.com.sg Principal Investigator: Deepak Mathur Sub-Investigator: Ban Leong Sng
Notes	Currently recruiting participants. Estimated Study Completion Date: July 2017

NCT02697929

Trial name or title	Sugammadex/neostigmine and liver transplantation
Methods	**Allocation:** randomized **Intervention model:** parallel assignment

NCT02697929 *(Continued)*

	Masking: no masking **Primary purpose:** prevention
Participants	**Estimated enrolment:** 40 **Inclusion criteria:** • 18 years of age and older • All sexes • ASA III status • Ability to give a written informed consent • Liver transplantation **Exclusion criteria:** • Any allergy to medications involved in the study • Any disease involving neuromuscular transmission • Any therapy with toremifene, flucloxacillin, or fusidic acid • Renal disease with glomerular filtration rate < 30 mL/min/1.73 m^2 • Hyperthermia maligna • Anticonceptional therapy • Pregnancy • Core body temperature < 35°C or skin temperature < 32°C at completion of surgery
Interventions	**Control group:** Neostigmine at completion of surgery: administration of 50 mcg/kg of neostigmine after third T2 twitch at TOF stimulation **Intervention group:** Sugammadex: at completion of surgery; administration of 2 mg/kg of sugammadex after third T2 twitch at TOF stimulation
Outcomes	**Primary outcome measures:** Recovery time from moderate neuromuscular block to TOFR > 0.9 after administration of sugammadex or neostigmine [Time Frame: 30 minutes] **Secondary outcome measures:** TOFR < 0.9 within 20 minutes after extubation [Time Frame: 20 minutes]
Starting date	January 2014
Contact information	Azienda Ospedaliera S. Maria della Misericordia, Udine, Italy, Principal Investigator: Livia Pompei; livia.pompei@uniud.it Study Director: Giorgio Della Rocca; giorgio.dellarocca@uniud.it
Notes	Currently recruiting participants. Estimated Study Completion Date: March 2017

NCT02698969

Trial name or title	Recovery of muscle function after deep neuromuscular block by means of diaphragm ultrasonography
Methods	**Allocation:** randomized **Endpoint classification:** efficacy study **Intervention model:** parallel assignment **Masking:** double-blind (participant, caregiver) **Primary purpose:** treatment
Participants	**Estimated enrolment:** 58 **Inclusion criteria:** • ASA physical status I to II • Between 18 and 80 years old • dNMB with rocuronium during ear nose and throat (ENT) surgery **Exclusion criteria:** • Clinical diagnosis of hepatic or renal disease • Clinical diagnosis of chronic or acute alcoholism • History of allergy or hypersensitivity to sugammadex and/or atropine or neostigmine • Current medications with CNS effects • History of neurological disease • Diaphragmatic palsy • Pregnancy or nursing • History of malignant arrhythmias
Interventions	Sugammadex 2 $mg*kg^{-1}$ at completion of surgery Neostigmine 50 $mcg*kg^{-1}$ and atropine 15 $mcg*kg^{-1}$ at completion of surgery
Outcomes	**Primary outcome measures:** • Number of participants with postoperative residual curarization (PORC) as assessed by diaphragm ultrasonography to determine its muscle strength [Time Frame: 30 minutes from completion of surgical procedure] [Designated as safety issue: yes] Clinician will assess TF (defined as a percentage) and amplitude of excursion (expressed in millimetres) of the diaphragm by means of ultrasonography **Secondary outcome measures:** • Number of participants with postoperative complications related to PORC such as pneumonia as assessed by chest x-ray and drop in SpO_2 as assessed by pulse oximeter and blood gas sample [Time Frame: up to 1 week] [Designated as safety issue: yes] • Number of participants with PONV as assessed by postoperative nausea and vomiting visual analogue scale (PONV VAS) [Time Frame: up to 48 hours] [Designated as safety issue: yes]
Starting date	November 2014
Contact information	Chiara Adembri, MD, +390554271101: chiara.adembri@unifi.it Azienda Ospdaliero Universitaria Careggi Principal Investigator: Chiara Adembri, MD

NCT02698969 *(Continued)*

	Sub-Investigator: Iacopo Cappellini, MD Sub-Investigator: Daniele Ostento, MD Sub-Investigator: Fabio Picciafuochi, MD
Notes	This study is currently recruiting participants. Estimated Study Completion Date: July 2017

NCT02845375

Trial name or title	Effect of neuromuscular blockade and reversal on breathing (BREATH)
Methods	**Allocation:** randomized **Endpoint classification:** pharmacodynamics study **Intervention model:** parallel assignment **Masking:** double-blind (participant, investigator, outcomes assessor) **Primary purpose:** treatment
Participants	**Estimated enrolment:** 30 **Inclusion criteria:** • Male gender • Age 18 years and older • BMI < 30 kg/m^2 **Exclusion criteria:** • Known or suspected neuromuscular disorders impairing neuromuscular function • Allergy to muscle relaxants, anaesthetics, or narcotics • (Family) history of malignant hyperthermia or any other muscle disease • Any medical, neurological, or psychiatric illness (including a history of anxiety)
Interventions	Placebo will be administered following a period of muscle relaxation after which respiratory measurements will be obtained Neostigmine will be administered following a period of muscle relaxation after which respiratory measurements will be obtained Sugammadex will be administered following a period of muscle relaxation after which respiratory measurements will be obtained
Outcomes	**Primary outcome measures:** • Ventilatory responses [Time Frame: during the 1 to 2 hours following reversal] [Designated as safety issue: no] Investigators will apply hypoxic and hypercapnic challenges and will measure ventilation on a breath-to-breath basis using the dynamic end-tidal forcing (DEF) technique. This technique allows manipulation of inspired gas concentrations to steer end-tidal concentrations of oxygen and carbon dioxide (CO_2) independent of the ventilatory response, or concentrations of O_2 and CO_2 in mixed venous blood. The technique allows reliable assessment of carotid body function (in this case, hypoxia) without the confounding effects of variations in end-tidal CO_2. Additionally, investigators will obtain the ventilatory response to hypercapnia at hyperoxic conditions. This allows assessment of the response activity of central chemoreceptors in the brainstem

NCT02845375 *(Continued)*

Starting date	September 2016
Contact information	Leiden University Medical Center, Leiden, ZH, Netherlands, 2333 ZA
Notes	This study is not yet open for participant recruitment

NCT02860507

Trial name or title	Study to determine if administration of sugammadex impacts hospital efficiency
Methods	**Allocation:** randomized **Endpoint classification:** efficacy study **Intervention model:** parallel assignment **Masking:** double-blind (participant, caregiver, investigator, outcomes assessor) **Primary purpose:** treatment
Participants	**Estimated enrolment:** 50 **Inclusion criteria:** • Scheduled for open ventral hernia repair or open colectomy • ASA class I to III • ≥ 18 years of age • Body mass index (BMI) < 45 kg/m^2 and weight < 150 kg • Written informed consent **Exclusion criteria:** • Medical conditions and/or surgical procedures that are not compatible with use of the TOF-Watch SX (e.g. injuries to the thumbs/distal forearms, bilateral ulnar nerve damage, cardiac pacemaker) • Known or suspected neuromuscular disorders impairing neuromuscular blockade (e.g. myasthenia gravis) • Known or suspected significant renal dysfunction (e.g. creatinine clearance < 30 mL.min^{-1}) • Known or suspected family history of malignant hyperthermia; significant hepatic dysfunction • Known or suspected allergy to opiates/opioids, muscle relaxants, or other medications used during general anaesthesia • Known or suspected hypersensitivity to sugammadex or other cyclodextrins or rocuronium or any of its excipients • Contraindication to rocuronium or sugammadex • Pregnancy • Morbid obesity with BMI > 45 kg/m^2 or weight > 150 kg
Interventions	Neostigmine 0.06 mg/kg and glycopyrrolate 0.04 mg/kg IV Sugammadex 4 mg/kg
Outcomes	**Primary outcome measures:** • Operating room (OR) turnover time when sugammadex is used instead of combination of neostigmine and glycopyrrolate [Time Frame: through start of next surgery, average of 2 hours] [Designated as safety issue: no] **Secondary outcome measures:**

NCT02860507 *(Continued)*

	• Number of participants who experience postoperative nausea and vomiting, postoperative pain, and postoperative complications [Time Frame: through discharge from hospital, average of 72 hours] [Designated as safety issue: no]
Starting date	August 2016
Contact information	Enrico Camporesi, Attending Anesthesiologist & Director of Research, SE, University of South Florida
Notes	This study is enrolling participants by invitation only. Estimated Primary Completion Date: May 2017

NCT02861131

Trial name or title	The effect of sugammadex versus neostigmine on postoperative pulmonary complications
Methods	**Allocation:** randomized **Endpoint classification:** safety/efficacy study **Intervention model:** parallel assignment **Masking:** open-label **Primary purpose:** prevention
Participants	**Estimated enrolment:** 200 **Inclusion criteria:** • Age ≥ 70 years • Elective surgery Monday through Friday in the South Operating Rooms of Oregon Health and Science University (OHSU) • Planned general endotracheal anaesthesia • Expected surgical duration ≥ 3 hours **Exclusion criteria:** • Prisoner • Inability to consent for surgery or anaesthesia • Surgery for which neuromuscular blockade is contraindicated (e.g. neurosurgical, orthopaedic, head and neck surgery, in which nerve monitoring will be employed) • Known neuromuscular disorder • Stage 4 chronic kidney disease or worse (estimated glomerular filtration rate < 30 mL/min) • Liver disease • Allergy to sugammadex, rocuronium, neostigmine, or glycopyrrolate • Taking toremifene
Interventions	Sugammadex 2 mg/kg IV once at completion of surgery Neostigmine 0.07 mg/kg to maximum of 5 mg (+ glycopyrrolate 0.1 to 0.2 mg per 1 mg of neostigmine administered) IV once at completion of surgery
Outcomes	**Primary outcome measures:** • Postoperative pulmonary complications [Time Frame: Length of hospitalizations, average 1 week] [Designated as safety issue: yes] A composite outcome that includes any of the following: post-

NCT02861131 *(Continued)*

	operative pneumonia, aspiration pneumonitis, atelectasis, pneumothorax, desaturation/hypoxaemia, upper airway obstruction, or acute respiratory insufficiency **Secondary outcome measures:** • Proportion of participants with residual neuromuscular blockade in the PACU [Time Frame: 1 day] [Designated as safety issue: yes] Residual neuromuscular blockade will be defined as TOFR < 0.9 taken within 5 minutes of arrival in the PACU • PACU phase 1 recovery time [Time Frame: 1 day] **Other outcome measures:** • Hospital length of stay [Time Frame: Length of hospitalization, average 1 week] [Designated as safety issue: no] • Proportion of participants who require hospital readmission for any cause within 4 weeks of hospital discharge [Time Frame: Length of hospitalization plus 4 weeks post discharge] [Designated as safety issue: yes] • Proportion of eligible patients diagnosed with a respiratory complication defined in the national surgical quality improvement program (NSQIP) [Time Frame: Length of hospitalization, average 1 week] [Designated as safety issue: yes] Pneumonia, unplanned re-intubation for any reason other than a return trip to the operating room, and ventilator times greater than 48 hours - excluding operating room time
Starting date	Study Start Date: November 2016 Estimated Study Completion Date: May 2018
Contact information	Contact: Miriam Treggiari, MD, PhD, MPH; 503-494-7229 treggiar@ohsu.edu Contact: Nabil J Alkayed, MD; 503-494-7229 alkayedn@ohsu.edu Principal Investigator: Brandon M Togioka, MD Sub-Investigator: Michael Aziz, MD Sub-Investigator: Miriam Treggiari, MD, PhD, MPH Oregon Health and Science University
Notes	This study is not yet open for participant recruitment

NCT02909439

Trial name or title	Quality of recovery after reversal with neostigmine or sugammadex
Methods	**Allocation:** randomized **Intervention model:** parallel assignment **Masking:** outcomes assessor **Primary purpose:** treatment
Participants	**Estimated enrolment:** 80 **Inclusion criteria:**

NCT02909439 *(Continued)*

	• Willing and able to provide written informed consent for the study • ≥ 18 years of age • ASA class I, II, or III • Planned use of neuromuscular blocking drugs • Planned use of endotracheal intubation • Planned extubation to occur in the OR **Exclusion criteria:** • ASA class IV • < 18 years old • Inability to give oral or written consent • Known or suspected neuromuscular disorder impairing neuromuscular function • True allergy to muscle relaxants • (Family) history of malignant hyperthermia • Contraindication for neostigmine or sugammadex administration • Serum creatinine level > 2.0 mg/dL • Surgery during which patient's arm is not available for neuromuscular monitoring • Plan to extubate under deep anaesthesia • Pregnancy
Interventions	**Control group:** Participants in this arm will receive neostigmine for reversal of neuromuscular blockade. No further details **Intervention group:** Participants in this arm will receive sugammadex for reversal of neuromuscular blockade. No further details.
Outcomes	**Primary outcome measures:** • Incentive spirometry, change from baseline, and recovery profile will be measured **Secondary outcome measures:** • Grip strength, change from baseline, and recovery profile will be measured with a hand dynamometer • Time to extubation. • Measured time between completion of surgery and time of extubation (removal of breathing tube) • Time to readiness for PACU discharge. • Measured time between PACU admission and meeting PACU discharge criteria. • TOFR upon PACU admission • Quality of recovery: 15-question survey to assess patient's overall quality of recovery after anaesthesia/surgery
Starting date	November 2016
Contact information	Stony Brook University Hospital,Stony Brook, New York, United States Contact: Sabeen Rizwan: sabeen.rizwan@stonybrookmedicine.edu Principal Investigator: Ramon Abola
Notes	Currently recruiting participants. Estimated Study Completion Date: September 2017

NCT02939430

Trial name or title	Sugammadex reversal of neuromuscular blockade and postoperative bleeding (Suga_bleeding)

NCT02939430 *(Continued)*

Methods	**Allocation:** randomized **Intervention model:** parallel assignment **Masking:** participant, investigator **Primary purpose:** diagnostic
Participants	**Estimated enrolment:** 40 **Inclusion criteria:** • 20 to 60 years • All candidates for living donor liver transplantation **Exclusion criteria:** • Massive intraoperative bleeding manifestations of early graft dysfunction
Interventions	**Control group:** Reversal of neuromuscular blockade will be performed using classic drugs (neostigmine 80 mg/kg and atropine 40 mic/kg) **Intervention group:** Reversal of neuromuscular blockade will be performed using sugammadex 2 mg/kg
Outcomes	**Primary outcome measures:** • Activated partial thromboplastin time in seconds [Time Frame: 30 minutes] **Secondary outcome measures:** • International normalized ratio in seconds [Time Frame: 30 minutes]
Starting date	November 2016
Contact information	Mansoura University, Mansoura, Dkahleya, Egypt Contact: Alreafey Kandeel: refa3ey2@yahoo.com Contact: Amr M Yassen: amryassen@hotmail.com
Notes	Currently recruiting participants. Estimated Study Completion Date: October 2017

NCT03108989

Trial name or title	Comparison of the postoperative quality of recovery between neostigmine and sugammadex in elderly patients undergoing trans pars plana vitrectomy with general anesthesia
Methods	**Allocation:** randomized **Intervention model:** parallel assignment **Masking:** participant, outcomes assessor **Primary purpose:** prevention
Participants	**Estimated enrolment:** 40

NCT03108989 *(Continued)*

	Inclusion criteria: • Adult > 60 years of age who are scheduled for trans pars plana vitrectomy with general anaesthesia **Exclusion criteria:** • Neuromuscular disease • History of malignant hyperthermia • Significant renal or hepatic dysfunction • Allergy to sugammadex or rocuronium • BMI > 30 kg/m^2 • History of medication that affects neuromuscular blocker such as anticonvulsants, magnesium
Interventions	**Control group:** After completion of surgery, neostigmine will be administered to reverse neuromuscular blockade. **Intervention group:** After completion of surgery, sugammadex 2 mg/kg will be administered to reverse neuromuscular blockade.
Outcomes	**Primary outcome measures:** • Physiological domain of PQRS recovery [Time Frame: at 40 minutes after completion of surgery] • Primary objective of the study was to assess the physiological domain of PQRS recovery from anaesthesia for patients treated with neostigmine and for those given sugammadex 40 minutes after completion of surgery. Recovery was defined as return to (or improvement from) baseline values. **Secondary outcome measures:** • Overall PQRS recovery and recovery in different domains of the PQRS [Time Frame: Secondary objective of the study was to compare overall PQRS recovery and recovery in different domains of the PQRS between participants treated with neostigmine and sugammadex at 15 minutes, 40 minutes, and 1 day after completion of surgery] at 15 minutes, 40 minutes, and 1 day after completion of surgery
Starting date	8 February 2017
Contact information	Republic of Korea, Seoul, Yonsei University, Department of Anesthesiology and Pain Medicine. Contact: Sun Joon Bai: SJBAE@yuhs.ac
Notes	Currently recruiting participants. Estimated Study Completion Date: 31 October 2017

NCT03116997

Trial name or title	Study of recovery of strength after surgery comparing two different medications for reversal of muscle relaxant
Methods	**Allocation:** randomized **Intervention model:** parallel assignment **Masking:** participant, outcomes assessor **Primary purpose:** treatment
Participants	**Estimated enrolment:** 202

NCT03116997 *(Continued)*

	Inclusion criteria: • ≥ 18 years of age and capable of giving consent • Undergoing surgical procedures with expected length of 6 or fewer hours requiring NMB **Exclusion criteria:** • Pregnancy • History of documented anaphylaxis or contraindication to any of the study medications • Surgical procedure for which both arms are required to be tucked at the patient's side • Active coronary disease with a positive cardiac stress test • History of severe chronic obstructive pulmonary disease (COPD) defined as FEV_1 < 50% of predicted • Serum creatinine ≥ 2.0 mg/dL • Severe hepatic dysfunction accompanied by coagulopathy • Chronic sustained release opioid use preop for longer than 2 weeks • Use of toremifene • Significant cognitive impairment or documented psychological impairment • Myasthenia gravis or other neuromuscular disease • Not eligible for standard anaesthetic induction (e.g. needing rapid sequence induction or awake fiberoptic bronchial intubation) • ASA status > III
Interventions	**Control group:** At conclusion of surgery, neuromuscular blockade reversed with neostigmine/glycopyrrolate **Intervention group:** At conclusion of surgery, neuromuscular blockade reversed with sugammadex
Outcomes	**Primary outcome measures:** • Measure participants' recovery time post surgery [Time Frame: 1 day] • Determine whether sugammadex as compared with neostigmine decreases time for patients to be ready for discharge from the PACU post surgery
Starting date	7 April 2017
Contact information	United States, New Jersey Memoral Sloan Kettering Basking Ridge, Basking Ridge, New Jersey, United States United States, New York Memorial Sloan Kettering Cancer Center, Commack, New York, United StatesMemoral Sloan Kettering Westchester, Harrison, New York, United States Memorial Sloan Kettering Cancer Center, New York, New York, United States Contact: German Echeverry: echeverg@mskcc.org
Notes	Currently recruiting participants. Estimated Study Completion Date: April 2019

NCT03144453

Trial name or title	Recovery from anesthesia after robotic assisted radical cystectomy
Methods	**Allocation:** randomized

NCT03144453 *(Continued)*

	Intervention model: parallel assignment **Masking:** participant, care provider, investigator, outcomes assessor **Primary purpose:** treatment
Participants	**Estimated enrolment:** 50 **Inclusion criteria:** • ≥ 18 years of age • ASA score ≤ III • Underwent robotic assisted cystectomy **Exclusion criteria:** • Cerebrovascular disease • BMI (body mass index) ≥ 30
Interventions	**Control group:** Participants received neostigmine + atropine as neuromuscular blockade reversal **Interventions group:** Participants received sugammadex as neuromuscular blockade reversal
Outcomes	**Primary outcome measures:** • Time to discharge from recovery room [Time Frame: up to 240 minutes after recovery] • Time between reversal administration and discharge from recovery room
Starting date	2 May 2017
Contact information	Ester Forastierem Rome, Italy Contact: Ester Forastiere: ester.forastiere@ifo.gov.it Regina Elena Cancer Institute, Rome,Italy Contact: Forastiere Ester: forastiere@ifo.it Sub-Investigator: Claudia Claroni
Notes	Currently recruiting participants. Estimated Study Completion Date: November 2017

List of acronyms and abbreviations used in these tables

ASA - American Society of Anesthesiology; BMI - body mass index; CI - confidence interval; CNS - central nervous system; COPD - chronic obstructive pulmonary disease; CrCL - creatinine clearance; DEF – dynamic end-tidal forcing; DL – diffusion lung capacity; DLCO/VA – diffusion lung capacity for carbon monoxide/alveolar volume ratio; dNMB – deep neuromuscular blockage; eGFR - estimated glomerular filtration rate;

ENT – ear, nose, and throat; FEV_1 – forced expiratory volume in one second; FiO_2 - fraction of inspired oxygen; FVC – functional vital capacity; GCS – Glasgow Coma Scale; GOLD – Global initiative for Chronic Obstructive Lung Disease; Hb - haemoglobin; IU/L – international unit/litre; ICU - intensive care unit; IU/L - international units/litre; IV - intravenous; MedDRA - Medical Dictionary for Regulatory Activities; MELD - model for end-stage liver disease; METS - metabolic equivalent of tasks; NMB - neuromuscular blocking; NMBA - neuromuscular blocking agent; NSQIP - national surgical quality improvement program; OR - operations room; PaCO2 - partial pressure of carbon dioxide; PACU - post anaesthesia care unit; PADSS - post anaesthesia discharge score system; PaO_2 - partial pressure of oxygen in blood; PEF - peak expiratory flow; pO_2 - partial pressure of oxygen; PONV - postoperative nausea and vomiting; PTC - post-tetanic count; PQRS - postoperative quality recovery scale; SpO_2 - peripheral oxygen saturation; Sq - square; SRS - surgical rating score; TOF - train of four; TOFR - train-of-four ratio; VA - alveolar volume; VAS - visual analogue scale

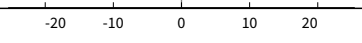
DATA AND ANALYSES

Comparison 1. Sugammadex 2.0 mg/kg vs neostigmine 0.05 mg/kg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recovery time from T2 to TOFR > 0.9	10	835	Mean Difference (IV, Random, 95% CI)	-10.22 [-11.96, -8.48]
2 Subgroup analysis: TIVA vs volatile anaesthetics	11	871	Mean Difference (IV, Random, 95% CI)	-9.83 [-11.45, -8.20]
2.1 TIVA	3	381	Mean Difference (IV, Random, 95% CI)	-8.50 [-10.15, -6.86]
2.2 Volitile anaesthetics	8	490	Mean Difference (IV, Random, 95% CI)	-10.57 [-12.96, -8.18]
3 Sensitivity analysis: meeting abstracts excluded	9	767	Mean Difference (IV, Random, 95% CI)	-9.27 [-11.14, -7.40]

Analysis 1.1. Comparison 1 Sugammadex 2.0 mg/kg vs neostigmine 0.05 mg/kg, Outcome 1 Recovery time from T2 to TOFR > 0.9.

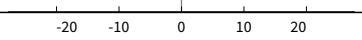
Study or subgroup	Sugammadex N	Sugammadex Mean(SD)	Neostigmine N	Neostigmine Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Blobner 2010	47	1.4 (1.1)	45	18.5 (25.8)		3.71%	-17.1[-24.64,-9.56]
Cheong 2015	30	3 (1.5)	30	15.9 (6.3)		10.08%	-12.9[-15.23,-10.57]
Foletto 2014	17	1.6 (0.4)	17	9.9 (4)		10.71%	-8.3[-10.21,-6.39]
Gaszynski 2011	35	2.7 (1)	35	9.6 (3.8)		11.51%	-6.89[-8.18,-5.6]
Georgiou 2013	13	2.3 (1.8)	15	13.4 (6.1)		8.67%	-11.06[-14.27,-7.85]
Georgiou 2013	15	2.4 (1.5)	14	12 (6.8)		7.97%	-9.53[-13.19,-5.87]
Grintescu 2009	17	1.2 (0.8)	17	16.7 (6.9)		8.52%	-15.5[-18.8,-12.2]
Illman 2011	24	1.7 (0.7)	23	13.3 (5.7)		10.04%	-11.6[-13.95,-9.25]
Koc 2015	16	2.3 (0.9)	17	9.4 (2.7)		11.43%	-7.1[-8.46,-5.74]
Woo 2013	59	1.5 (1.8)	59	14.5 (19.1)		6.22%	-12.99[-17.89,-8.09]
Wu 2014	148	1.4 (0.9)	142	8.4 (9.6)		11.15%	-7.01[-8.6,-5.42]
Total * **	**421**		**414**			**100%**	**-10.22[-11.96,-8.48]**
Heterogeneity: Tau²=6.41; Chi²=62, df=10(P<0.0001); I²=83.87%							
Test for overall effect: Z=11.51(P<0.0001)							



Favours [Sugammadex] Favours [Neostigmine]

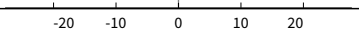
Analysis 1.2. Comparison 1 Sugammadex 2.0 mg/kg vs neostigmine 0.05 mg/kg, Outcome 2 Subgroup analysis: TIVA vs volatile anaesthetics.

Study or subgroup	Sugammadex N	Sugammadex Mean(SD)	Neostigmine N	Neostigmine Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.2.1 TIVA							



Favours [Sugammadex] Favours [Neostigmine]

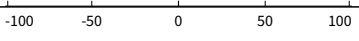
Study or subgroup	Sugammadex N	Sugammadex Mean(SD)	Neostigmine N	Neostigmine Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Foletto 2014	17	1.6 (0.4)	17	9.9 (4)		9.72%	-8.3[-10.21,-6.39]
Georgiou 2013	15	2.4 (1.5)	14	12 (6.8)		7.16%	-9.53[-13.19,-5.87]
Georgiou 2013	13	2.3 (1.8)	15	13.4 (6.1)		7.81%	-11.06[-14.27,-7.85]
Wu 2014	148	1.4 (0.9)	142	8.4 (9.6)		10.13%	-7.01[-8.6,-5.42]
Subtotal ***	**193**		**188**			**34.82%**	**-8.5[-10.15,-6.86]**
Heterogeneity: Tau²=1.28; Chi²=5.71, df=3(P=0.13); I²=47.43%							
Test for overall effect: Z=10.15(P<0.0001)							
1.2.2 Volitile anaesthetics							
Blobner 2010	47	1.4 (1.1)	45	18.5 (25.8)		3.29%	-17.1[-24.64,-9.56]
Cheong 2015	30	3 (1.5)	30	15.9 (6.3)		9.13%	-12.9[-15.23,-10.57]
Gaszynski 2011	35	2.7 (1)	35	9.6 (3.8)		10.48%	-6.89[-8.18,-5.6]
Grintescu 2009	17	1.2 (0.8)	17	16.7 (6.9)		7.67%	-15.5[-18.8,-12.2]
Illman 2011	24	1.7 (0.7)	23	13.3 (5.7)		9.1%	-11.6[-13.95,-9.25]
Koc 2015	16	2.3 (0.9)	17	9.4 (2.7)		10.41%	-7.1[-8.46,-5.74]
Woo 2013	59	1.5 (1.8)	59	14.5 (19.1)		5.55%	-12.99[-17.89,-8.09]
Yagan 2015	18	3.3 (1.8)	18	9.5 (4)		9.57%	-6.25[-8.27,-4.23]
Subtotal ***	**246**		**244**			**65.18%**	**-10.57[-12.96,-8.18]**
Heterogeneity: Tau²=9.39; Chi²=60.75, df=7(P<0.0001); I²=88.48%							
Test for overall effect: Z=8.65(P<0.0001)							
Total ***	**439**		**432**			**100%**	**-9.83[-11.45,-8.2]**
Heterogeneity: Tau²=6.14; Chi²=66.85, df=11(P<0.0001); I²=83.55%							
Test for overall effect: Z=11.84(P<0.0001)							
Test for subgroup differences: Chi²=1.94, df=1 (P=0.16), I²=48.58%							



Favours [Sugammadex] Favours [Neostigmine]

Analysis 1.3. Comparison 1 Sugammadex 2.0 mg/kg vs neostigmine 0.05 mg/kg, Outcome 3 Sensitivity analysis: meeting abstracts excluded.

Study or subgroup	Sugammadex N	Sugammadex Mean(SD)	Neostigmine N	Neostigmine Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Adamus 2011	11	2 (0.5)	10	17 (38.9)		0.58%	-14.95[-39.06,9.16]
Blobner 2010	47	1.4 (1.1)	45	18.5 (25.8)		4.5%	-17.1[-24.64,-9.56]
Cheong 2015	30	3 (1.5)	30	15.9 (6.3)		13.4%	-12.9[-15.23,-10.57]
Gaszynski 2011	35	2.7 (1)	35	9.6 (3.8)		15.64%	-6.89[-8.18,-5.6]
Illman 2011	24	1.7 (0.7)	23	13.3 (5.7)		13.35%	-11.6[-13.95,-9.25]
Koc 2015	16	2.3 (0.9)	17	9.4 (2.7)		15.52%	-7.1[-8.46,-5.74]
Woo 2013	59	1.5 (1.8)	59	14.5 (19.1)		7.81%	-12.99[-17.89,-8.09]
Wu 2014	148	1.4 (0.9)	142	8.4 (9.6)		15.07%	-7.01[-8.6,-5.42]
Yagan 2015	18	3.3 (1.8)	18	9.5 (4)		14.13%	-6.25[-8.27,-4.23]
Total ***	**388**		**379**			**100%**	**-9.27[-11.14,-7.4]**
Heterogeneity: Tau²=5.38; Chi²=44.89, df=8(P<0.0001); I²=82.18%							
Test for overall effect: Z=9.72(P<0.0001)							



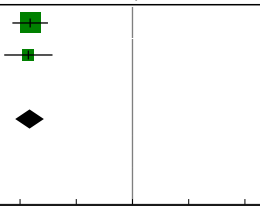
Favours [Sugammadex] Favours [Neostigmine]

Comparison 2. Sugammadex 4.0 mg/kg vs neostigmine 0.07 mg/kg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recovery time from PTC 1 to 5 to TOFR > 0.9	2	114	Mean Difference (IV, Random, 95% CI)	-45.78 [-52.15, -39.41]

Analysis 2.1. Comparison 2 Sugammadex 4.0 mg/kg vs neostigmine 0.07 mg/kg, Outcome 1 Recovery time from PTC 1 to 5 to TOFR > 0.9.

Study or subgroup	Sugammadex N	Sugammadex Mean(SD)	Neostigmine N	Neostigmine Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Carron 2013	20	3.1 (1.3)	20	48.6 (18)		64.81%	-45.5[-53.41,-37.59]
Jones 2008	37	2.7 (3.7)	37	49 (33.1)		35.19%	-46.3[-57.03,-35.57]
Total ***	**57**		**57**			**100%**	**-45.78[-52.15,-39.41]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.91); I^2=0%							
Test for overall effect: Z=14.09(P<0.0001)							



Comparison 3. Sugammadex (any dose) vs neostigmine (any dose)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk of composite adverse events	28	2298	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.49, 0.74]
2 Composite adverse events: subgroup analysis for dosage	28	2298	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.49, 0.73]
2.1 Sugammadex 2 mg/kg vs neostigmine 0.04 mg/kg	1	21	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.05, 4.28]
2.2 Sugammadex 2 mg/kg vs neostigmine 0.05 mg/kg	12	1076	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.34, 0.80]
2.3 Sugammadex 2 mg/kg vs neostigmine 0.07 mg/kg	2	131	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.57, 1.44]
2.4 Sugammadex 2 mg/kg vs neostigmine 2.5 mg	1	40	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Sugammadex 3 mg/kg vs neostigmine 0.03 mg/kg	1	90	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.6 Sugammadex 4 mg/kg vs neostigmine 0.05 mg/kg	4	333	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.49, 0.88]
2.7 Sugammadex 4 mg/kg vs neostigmine 0.07 mg/kg	3	197	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.25, 0.93]

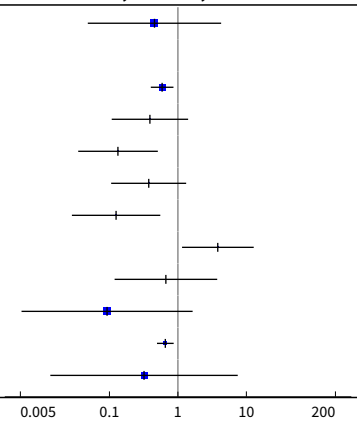
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.8 Sugammadex, several doses vs neostigmine, several doses	4	410	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.40, 0.90]
3 Composite adverse events: subgroup analysis - TIVA vs volatile anaesthetics	28	2298	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.49, 0.73]
3.1 TIVA	7	748	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.20, 1.31]
3.2 Volatile anaesthetic	20	1510	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.55, 0.73]
3.3 No information	1	40	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Composite adverse events: sensitivity analysis - excluding meeting abstracts	24	2091	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.49, 0.73]
5 Participants with ≥ adverse event	19	1766	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.48, 0.81]
6 Bradycardia: subgroup analysis - atropine vs glycopyrrolate	11	1218	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.07, 0.34]
6.1 Atropine	6	667	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.05, 0.36]
6.2 Glycopyrrolate	5	551	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.06, 0.69]
7 PONV: subgroup analysis - TIVA vs volatile anaesthetics	6	389	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.28, 0.97]
7.1 TIVA	1	94	Risk Ratio (M-H, Random, 95% CI)	3.55 [0.15, 84.86]
7.2 Volatile anaesthetics	5	295	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.25, 0.91]
8 Desaturation	2	134	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.06, 0.83]
9 Procedural complications	2	168	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.02, 0.97]
10 Transitory oxygen supplementation	2	76	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.09, 0.66]
11 Not able to perform 5 second head-lift after extubation	6	395	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.15, 0.78]
12 General muscle weakness after extubation	4	288	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.31, 1.18]

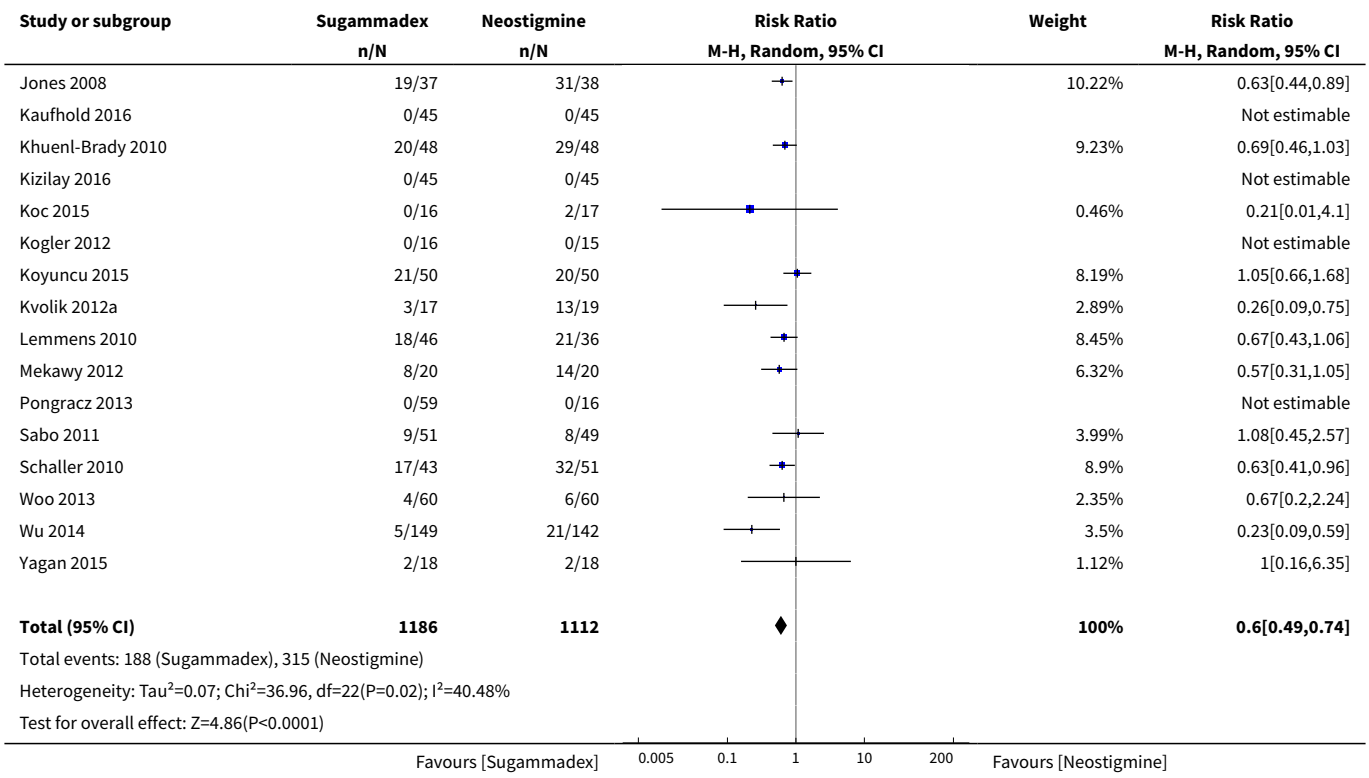
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Nausea	9	719	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.44, 1.56]
14 Vomiting	4	297	Risk Ratio (M-H, Random, 95% CI)	2.05 [0.50, 8.48]
15 Postprocedural nausea	2	168	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.27, 7.12]
16 Headache	4	388	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.48, 2.18]
17 Hypertension	3	287	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.23, 9.05]
18 Hypotension	4	465	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.38, 3.96]
19 Cough	3	200	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.42, 4.81]
20 Dry mouth	3	289	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.10, 1.87]
21 Dizziness	2	168	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.10, 9.23]
22 Tachycardia	3	338	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.09, 2.22]
23 Pruritus	2	175	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.20, 12.88]
24 Pyrexia	3	264	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.23, 8.91]
25 Shivering	3	190	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.40, 1.43]
26 Chills	2	166	Risk Ratio (M-H, Random, 95% CI)	4.04 [0.46, 35.85]
27 Rash	5	701	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.17, 3.96]
28 Supraventricular extrasystoles	2	189	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.03, 3.05]
29 Laryngospasm	2	100	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.07, 1.65]
30 Increased upper airway secretion	2	442	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.09, 1.59]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31 Procedural hypertension	3	267	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.33, 8.21]
32 Procedural hypotension	2	391	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.02, 14.15]
33 Abdominal pain	2	196	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.10, 9.27]
34 Clinical signs of residual NMB	7	646	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
35 Clinical signs of inadequate reversal of NMB	4	368	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 2.02]
36 Clinical signs of recurrence of residual NMB	13	1289	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.05, 10.74]
37 General muscle weakness at PACU discharge	5	410	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.12, 1.90]
38 Not able to perform 5 second head-lift at PACU discharge	5	399	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
39 Overall signs of postoperative residual paralysis	15	1474	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.28, 0.57]
40 Risk of composite serious adverse events	10	959	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.13, 2.25]
41 Participants with ≥ 1 serious adverse event	10	959	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.13, 2.25]

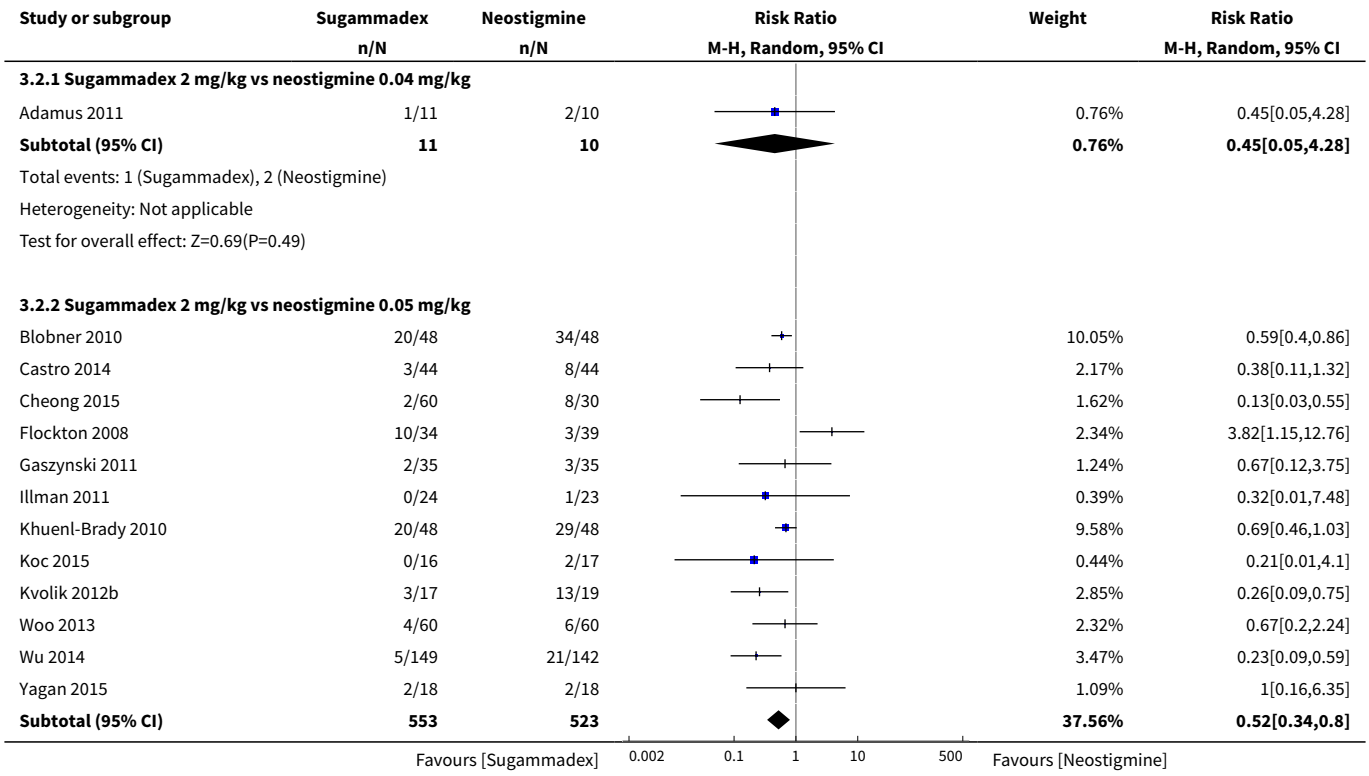
Analysis 3.1. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 1 Risk of composite adverse events.

Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adamus 2011	1/11	2/10		0.78%	0.45[0.05,4.28]
Balaka 2011	0/20	0/20			Not estimable
Blobner 2010	20/48	34/48		9.65%	0.59[0.4,0.86]
Brueckmann 2015	3/74	8/77		2.13%	0.39[0.11,1.41]
Carron 2013	2/20	15/20		1.99%	0.13[0.03,0.51]
Castro 2014	3/44	8/44		2.21%	0.38[0.11,1.32]
Cheong 2015	2/60	8/30		1.66%	0.13[0.03,0.55]
Flockton 2008	10/34	3/39		2.38%	3.82[1.15,12.76]
Gaszynski 2011	2/35	3/35		1.27%	0.67[0.12,3.75]
Geldner 2012	0/66	5/67		0.48%	0.09[0.01,1.64]
Hakimoglu 2016	19/30	29/30		11.43%	0.66[0.5,0.87]
Illman 2011	0/24	1/23		0.4%	0.32[0.01,7.48]

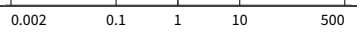


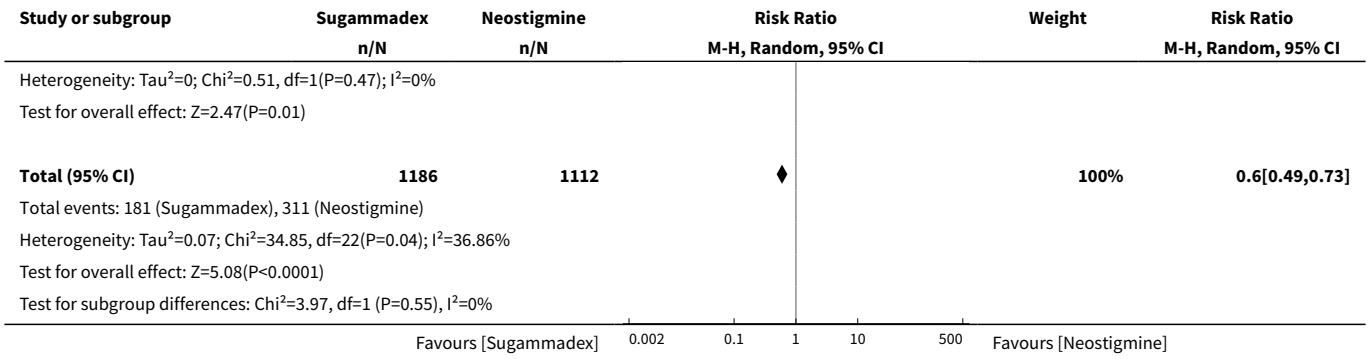


Analysis 3.2. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 2 Composite adverse events: subgroup analysis for dosage.

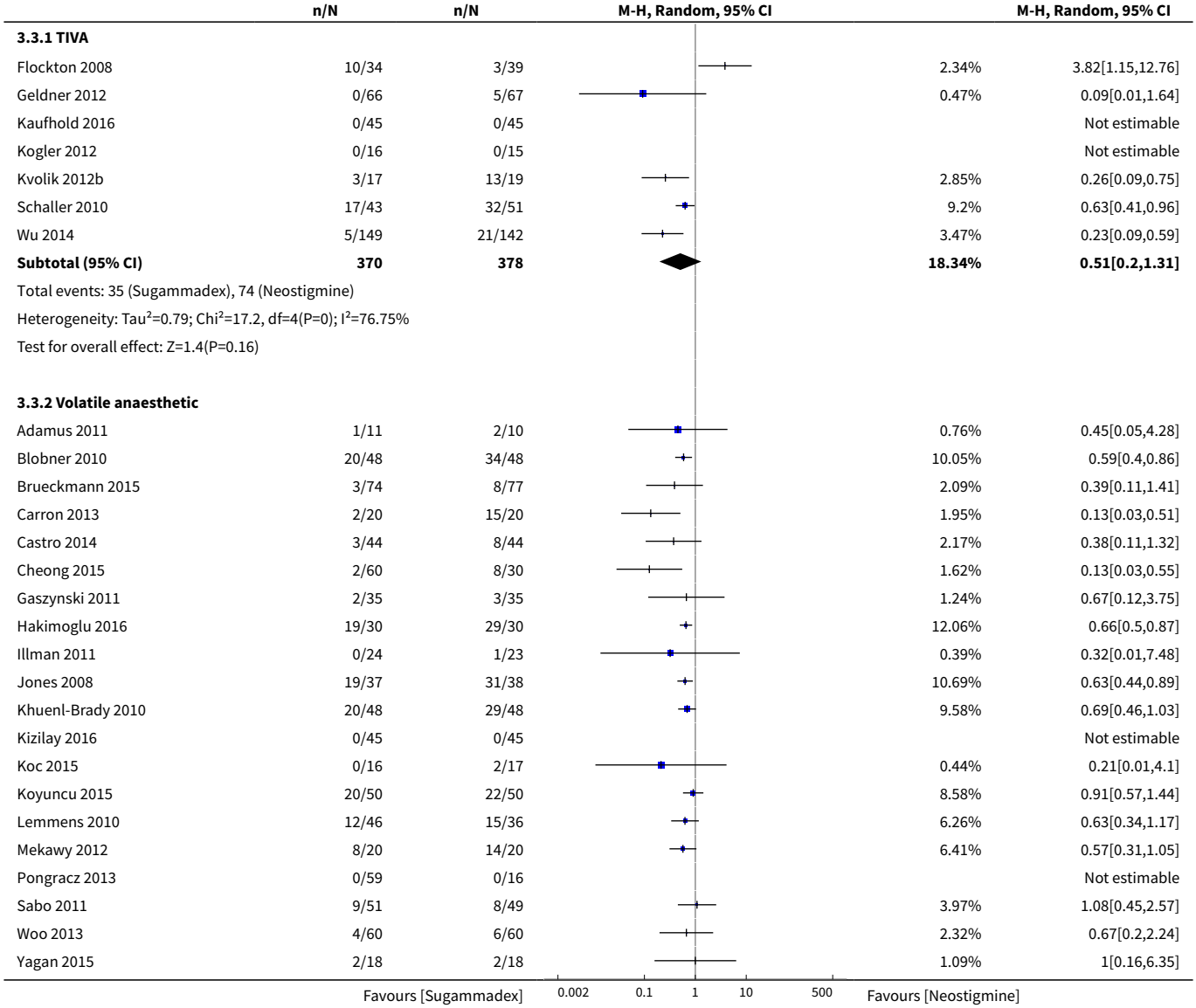


Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 71 (Sugammadex), 130 (Neostigmine)					
Heterogeneity: Tau²=0.21; Chi²=21.88, df=11(P=0.03); I²=49.72%					
Test for overall effect: Z=2.97(P=0)					
3.2.3 Sugammadex 2 mg/kg vs neostigmine 0.07 mg/kg					
Kogler 2012	0/16	0/15			Not estimable
Koyuncu 2015	20/50	22/50		8.58%	0.91[0.57,1.44]
Subtotal (95% CI)	**66**	**65**		**8.58%**	**0.91[0.57,1.44]**
Total events: 20 (Sugammadex), 22 (Neostigmine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.4(P=0.69)					
3.2.4 Sugammadex 2 mg/kg vs neostigmine 2.5 mg					
Balaka 2011	0/20	0/20			Not estimable
Subtotal (95% CI)	**20**	**20**			**Not estimable**
Total events: 0 (Sugammadex), 0 (Neostigmine)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.2.5 Sugammadex 3 mg/kg vs neostigmine 0.03 mg/kg					
Kizilay 2016	0/45	0/45			Not estimable
Subtotal (95% CI)	**45**	**45**			**Not estimable**
Total events: 0 (Sugammadex), 0 (Neostigmine)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.2.6 Sugammadex 4 mg/kg vs neostigmine 0.05 mg/kg					
Geldner 2012	0/66	5/67		0.47%	0.09[0.01,1.64]
Hakimoglu 2016	19/30	29/30		12.06%	0.66[0.5,0.87]
Mekawy 2012	8/20	14/20		6.41%	0.57[0.31,1.05]
Sabo 2011	9/51	8/49		3.97%	1.08[0.45,2.57]
Subtotal (95% CI)	**167**	**166**		**22.91%**	**0.66[0.49,0.88]**
Total events: 36 (Sugammadex), 56 (Neostigmine)					
Heterogeneity: Tau²=0.01; Chi²=3.3, df=3(P=0.35); I²=8.97%					
Test for overall effect: Z=2.83(P=0)					
3.2.7 Sugammadex 4 mg/kg vs neostigmine 0.07 mg/kg					
Carron 2013	2/20	15/20		1.95%	0.13[0.03,0.51]
Jones 2008	19/37	31/38		10.69%	0.63[0.44,0.89]
Lemmens 2010	12/46	15/36		6.26%	0.63[0.34,1.17]
Subtotal (95% CI)	**103**	**94**		**18.89%**	**0.49[0.25,0.93]**
Total events: 33 (Sugammadex), 61 (Neostigmine)					
Heterogeneity: Tau²=0.2; Chi²=5.69, df=2(P=0.06); I²=64.88%					
Test for overall effect: Z=2.18(P=0.03)					
3.2.8 Sugammadex, several doses vs neostigmine, several doses					
Brueckmann 2015	3/74	8/77		2.09%	0.39[0.11,1.41]
Kaufhold 2016	0/45	0/45			Not estimable
Pongracz 2013	0/59	0/16			Not estimable
Schaller 2010	17/43	32/51		9.2%	0.63[0.41,0.96]
Subtotal (95% CI)	**221**	**189**		**11.29%**	**0.6[0.4,0.9]**
Total events: 20 (Sugammadex), 40 (Neostigmine)					

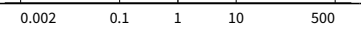




Analysis 3.3. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 3 Composite adverse events: subgroup analysis - TIVA vs volatile anaesthetics.

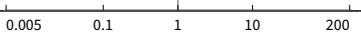


Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	**796**	**714**		**81.66%**	**0.64[0.55,0.73]**
Total events: 146 (Sugammadex), 237 (Neostigmine)					
Heterogeneity: Tau^2=0; Chi^2=17, df=17(P=0.45); I^2=0.01%					
Test for overall effect: Z=6.23(P<0.0001)					
3.3.3 No information					
Balaka 2011	0/20	0/20			Not estimable
Subtotal (95% CI)	**20**	**20**			**Not estimable**
Total events: 0 (Sugammadex), 0 (Neostigmine)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**1186**	**1112**		**100%**	**0.6[0.49,0.73]**
Total events: 181 (Sugammadex), 311 (Neostigmine)					
Heterogeneity: Tau^2=0.07; Chi^2=34.85, df=22(P=0.04); I^2=36.86%					
Test for overall effect: Z=5.08(P<0.0001)					
Test for subgroup differences: Chi^2=0.21, df=1 (P=0.64), I^2=0%					



Analysis 3.4. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 4 Composite adverse events: sensitivity analysis - excluding meeting abstracts.

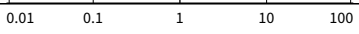
Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adamus 2011	1/11	2/10		0.76%	0.45[0.05,4.28]
Blobner 2010	20/48	34/48		10.98%	0.59[0.4,0.86]
Brueckmann 2015	3/74	8/77		2.14%	0.39[0.11,1.41]
Carron 2013	2/20	15/20		1.99%	0.13[0.03,0.51]
Castro 2014	3/44	8/44		2.22%	0.38[0.11,1.32]
Cheong 2015	2/60	8/30		1.65%	0.13[0.03,0.55]
Flockton 2008	10/34	3/39		2.4%	3.82[1.15,12.76]
Gaszynski 2011	2/35	3/35		1.25%	0.67[0.12,3.75]
Geldner 2012	0/66	5/67		0.47%	0.09[0.01,1.64]
Hakimoglu 2016	19/30	29/30		13.41%	0.66[0.5,0.87]
Illman 2011	0/24	1/23		0.4%	0.32[0.01,7.48]
Jones 2008	19/37	31/38		11.74%	0.63[0.44,0.89]
Kaufhold 2016	0/45	0/45			Not estimable
Khuenl-Brady 2010	20/48	29/48		10.42%	0.69[0.46,1.03]
Kizilay 2016	0/45	0/45			Not estimable
Koc 2015	0/16	2/17		0.45%	0.21[0.01,4.1]
Koyuncu 2015	20/50	22/50		9.26%	0.91[0.57,1.44]
Lemmens 2010	12/46	15/36		6.62%	0.63[0.34,1.17]
Mekawy 2012	8/20	14/20		6.79%	0.57[0.31,1.05]
Pongracz 2013	0/59	0/16			Not estimable
Schaller 2010	17/43	32/51		9.98%	0.63[0.41,0.96]
Woo 2013	4/60	6/60		2.37%	0.67[0.2,2.24]
Wu 2014	5/149	21/142		3.59%	0.23[0.09,0.59]
Yagan 2015	2/18	2/18		1.1%	1[0.16,6.35]



Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)	**1082**	**1009**		**100%**	**0.6[0.49,0.73]**
Total events: 169 (Sugammadex), 290 (Neostigmine)					
Heterogeneity: Tau^2=0.06; Chi^2=30.69, df=20(P=0.06); I^2=34.83%					
Test for overall effect: Z=5.02(P<0.0001)					

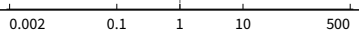
Analysis 3.5. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 5 Participants with ≥ adverse event.

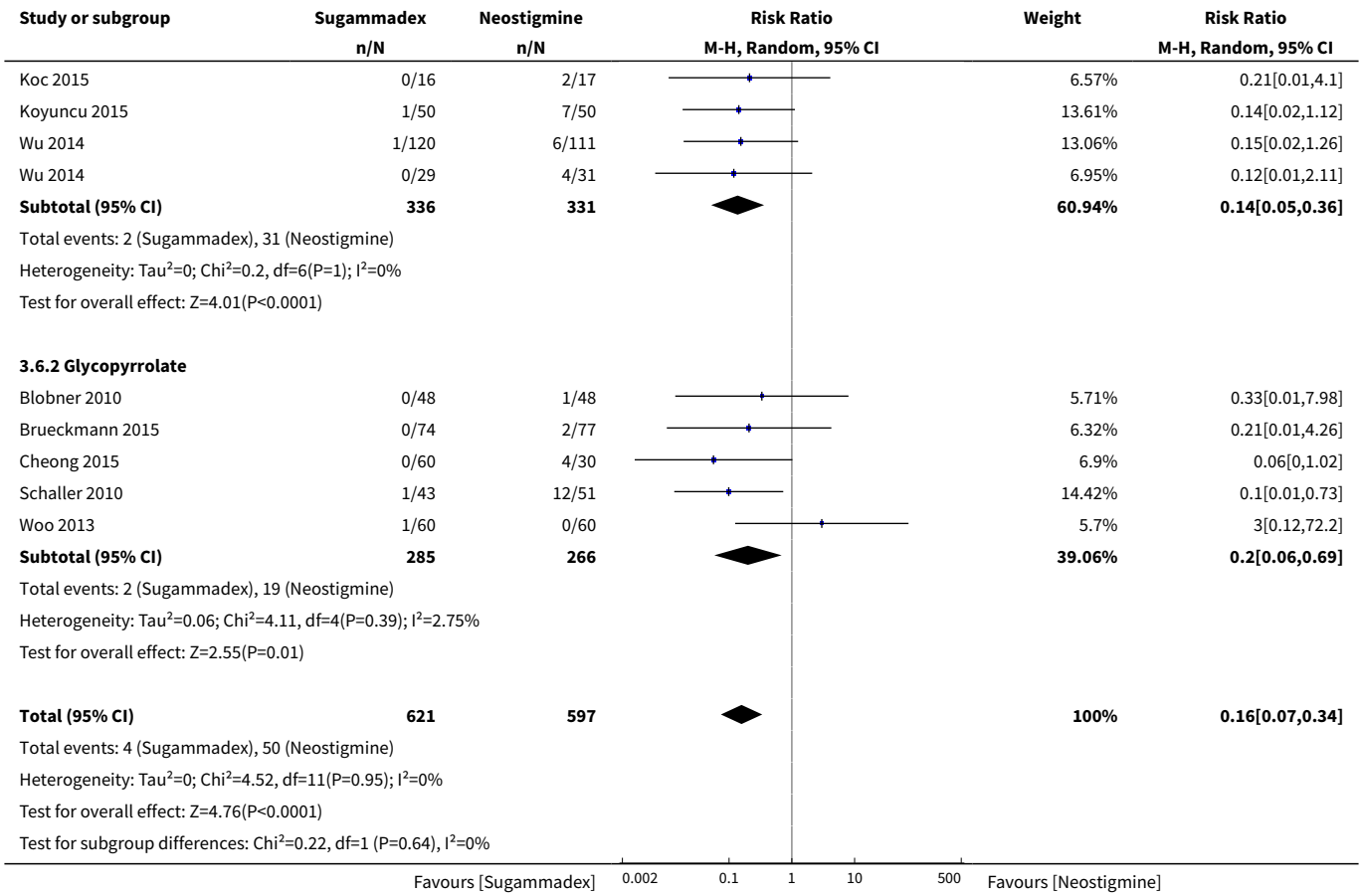
Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adamus 2011	1/11	2/10		1.39%	0.45[0.05,4.28]
Balaka 2011	0/20	0/20			Not estimable
Blobner 2010	7/48	10/48		9.07%	0.7[0.29,1.69]
Brueckmann 2015	4/74	10/77		5.64%	0.42[0.14,1.27]
Castro 2014	3/44	8/44		4.42%	0.38[0.11,1.32]
Flockton 2008	4/34	1/39		1.53%	4.59[0.54,39.1]
Gaszynski 2011	2/35	3/35		2.35%	0.67[0.12,3.75]
Geldner 2012	7/66	16/67		10.41%	0.44[0.2,1.01]
Illman 2011	0/24	1/23		0.71%	0.32[0.01,7.48]
Jones 2008	10/37	12/38		14.04%	0.86[0.42,1.73]
Kaufhold 2016	0/45	0/45			Not estimable
Khuenl-Brady 2010	7/48	10/45		9.13%	0.66[0.27,1.58]
Kizilay 2016	0/45	0/45			Not estimable
Kogler 2012	0/16	0/15			Not estimable
Lemmens 2010	9/46	10/36		11.29%	0.7[0.32,1.55]
Pongracz 2013	0/59	0/16			Not estimable
Sabo 2011	8/51	8/49		8.69%	0.96[0.39,2.36]
Woo 2013	4/60	6/60		4.76%	0.67[0.2,2.24]
Wu 2014	1/29	11/31		1.78%	0.1[0.01,0.71]
Wu 2014	11/120	20/111		14.77%	0.51[0.26,1.01]
Total (95% CI)	**912**	**854**		**100%**	**0.62[0.48,0.81]**
Total events: 78 (Sugammadex), 128 (Neostigmine)					
Heterogeneity: Tau^2=0; Chi^2=11.04, df=14(P=0.68); I^2=0%					
Test for overall effect: Z=3.55(P=0)					



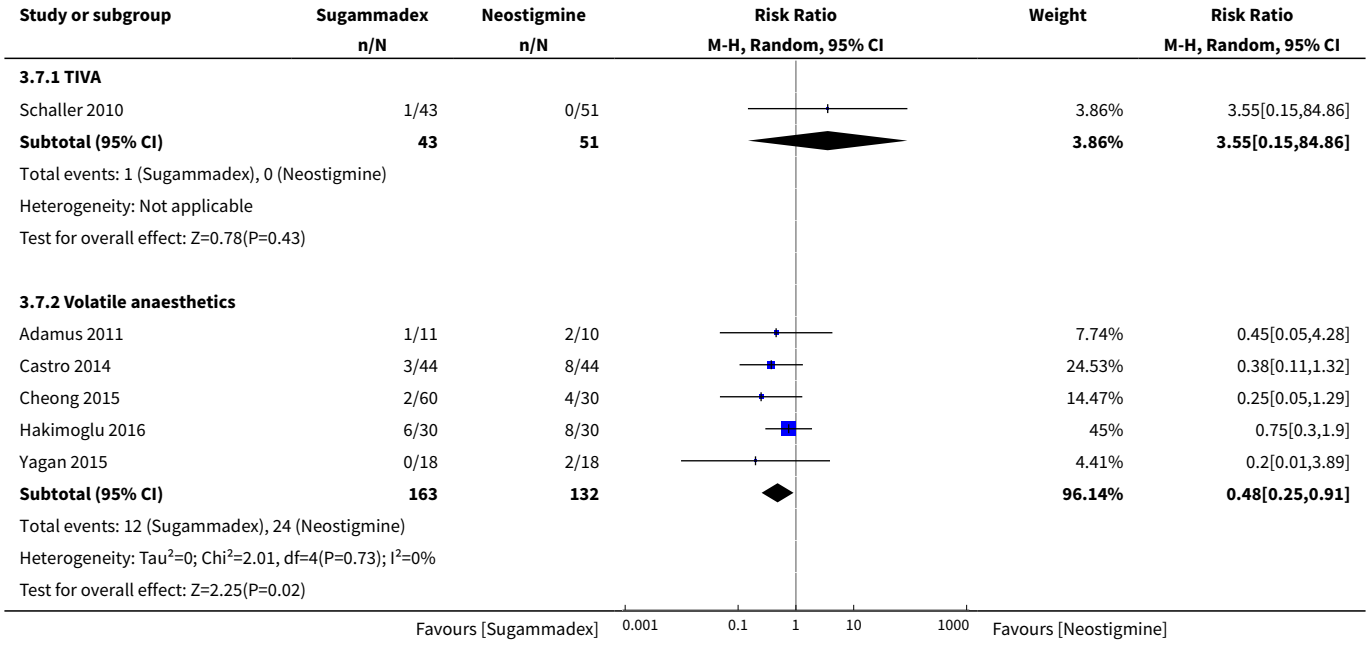
Analysis 3.6. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 6 Bradycardia: subgroup analysis - atropine vs glycopyrrolate.

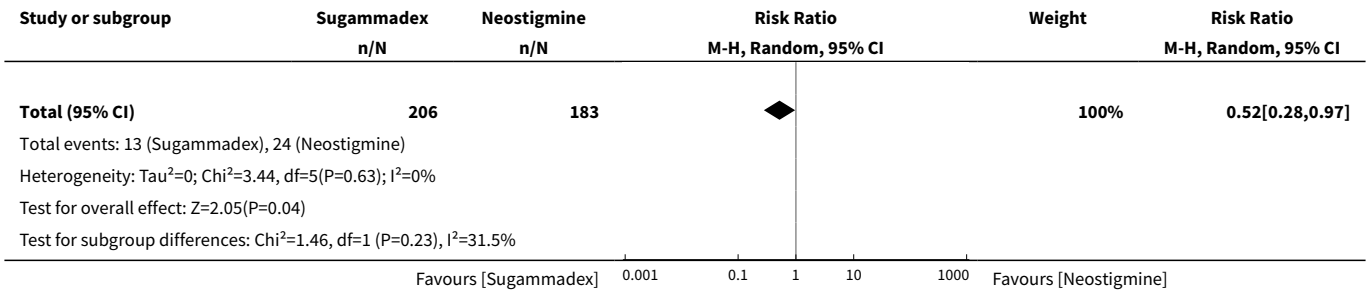
Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.6.1 Atropine					
Carron 2013	0/20	4/20		7.06%	0.11[0.01,1.94]
Gaszynski 2011	0/35	3/35		6.73%	0.14[0.01,2.67]
Geldner 2012	0/66	5/67		6.97%	0.09[0.01,1.64]



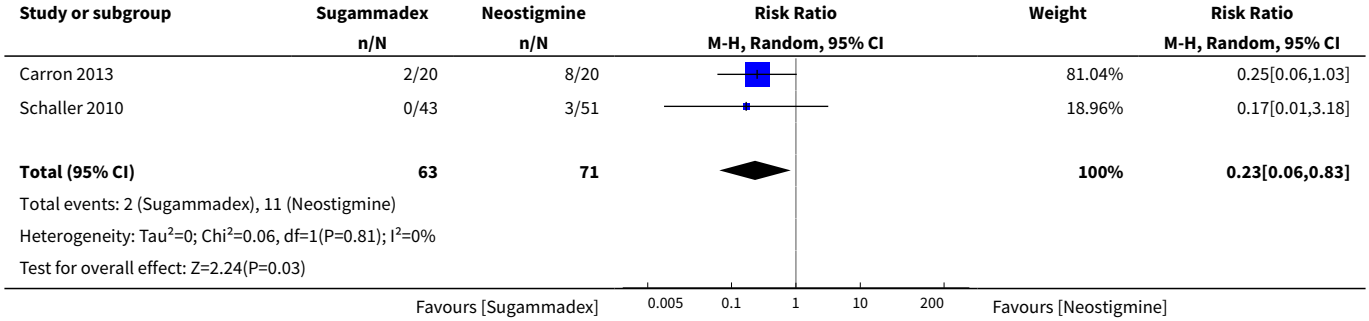


Analysis 3.7. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 7 PONV: subgroup analysis - TIVA vs volatile anaesthetics.

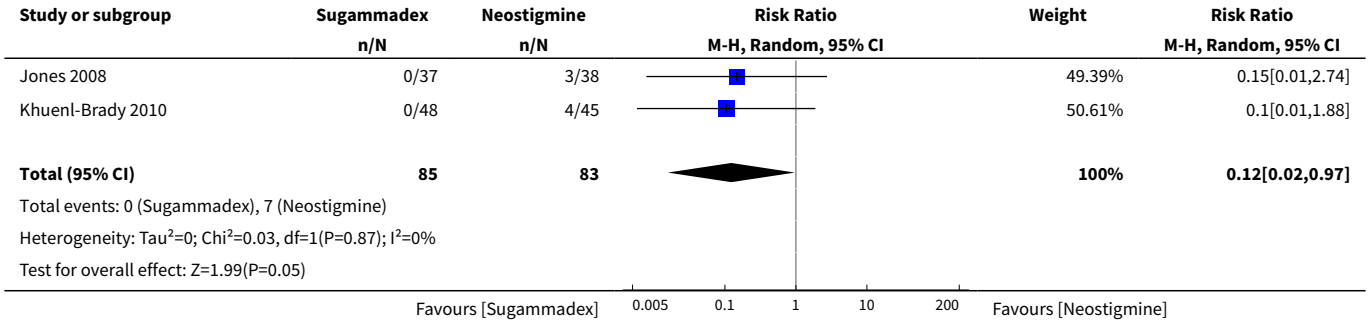




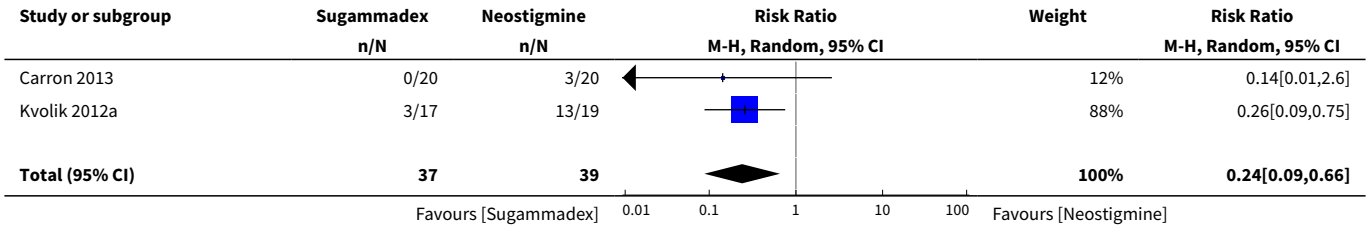
Analysis 3.8. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 8 Desaturation.

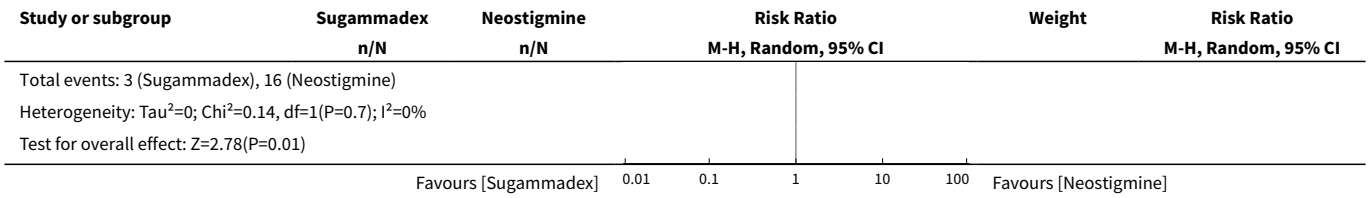


Analysis 3.9. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 9 Procedural complications.

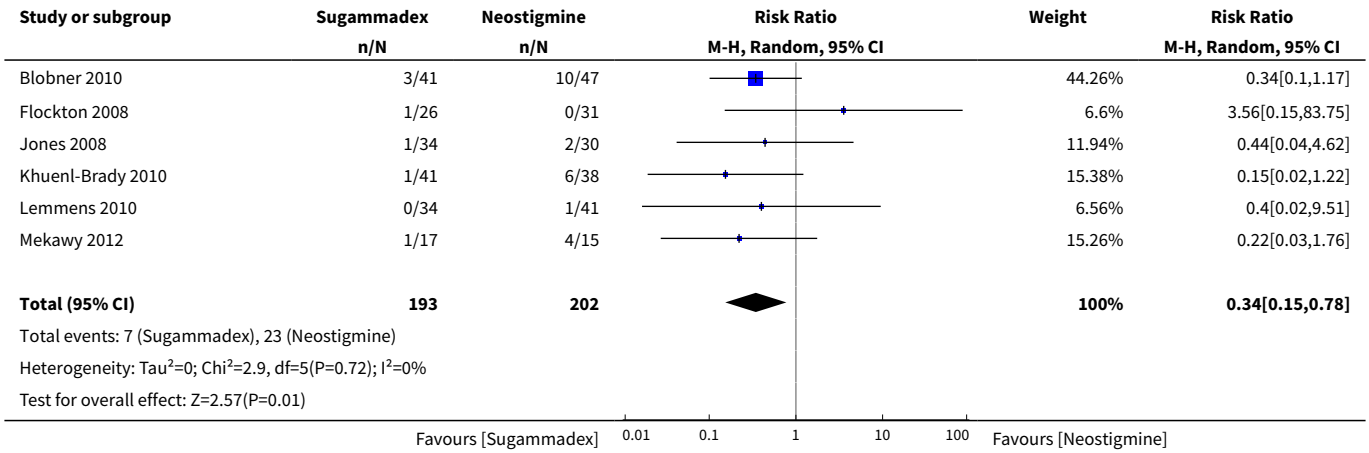


Analysis 3.10. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 10 Transitory oxygen supplementation.

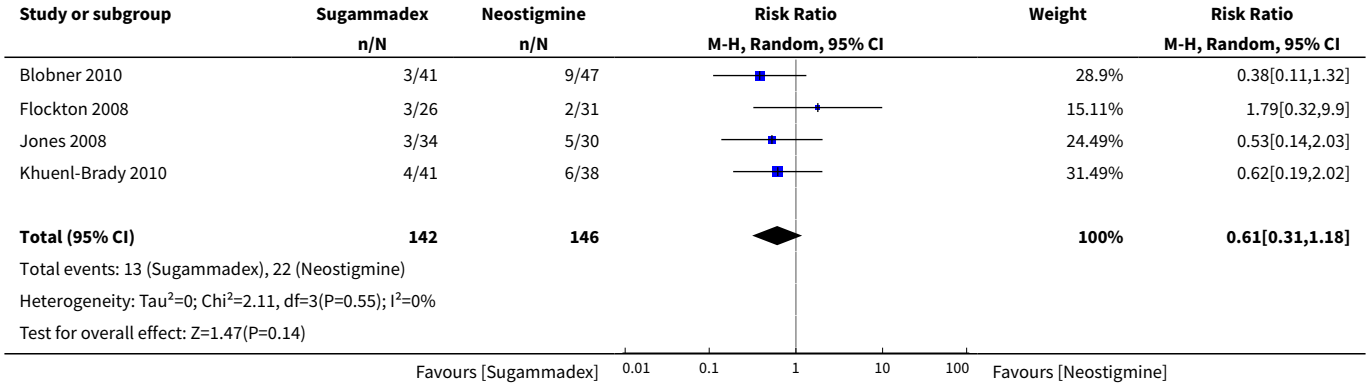




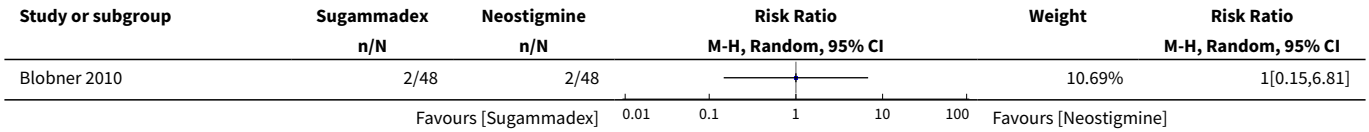
Analysis 3.11. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 11 Not able to perform 5 second head-lift after extubation.

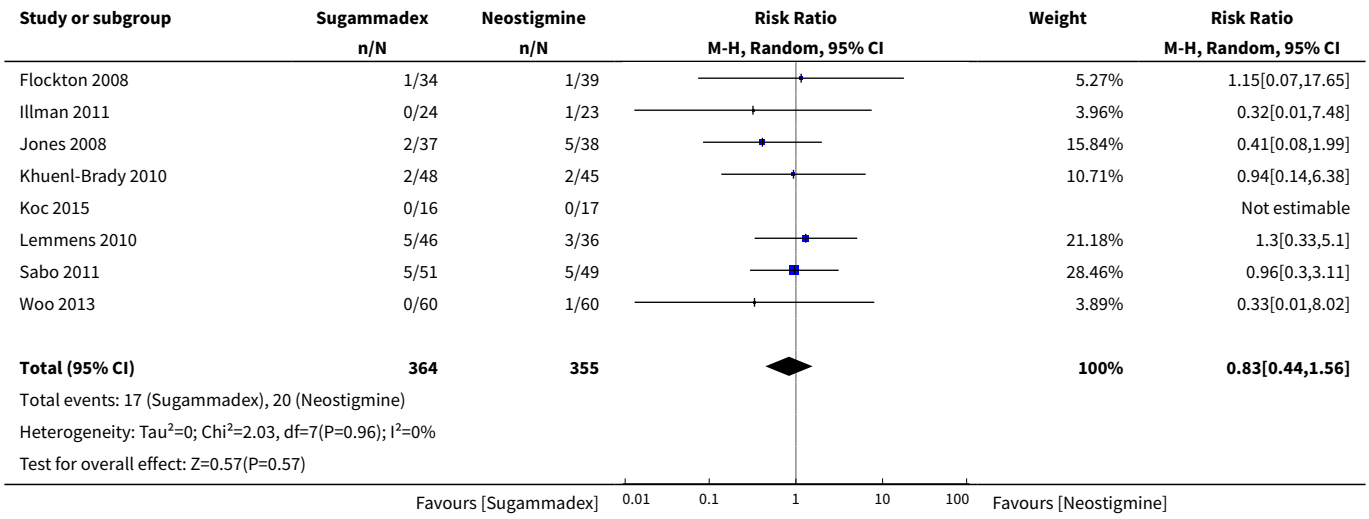


Analysis 3.12. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 12 General muscle weakness after extubation.

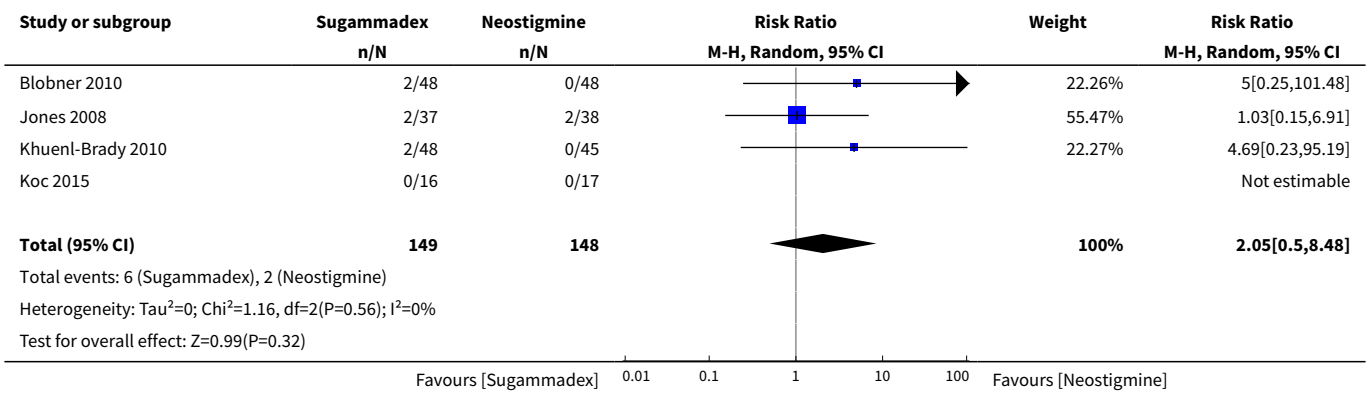


Analysis 3.13. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 13 Nausea.

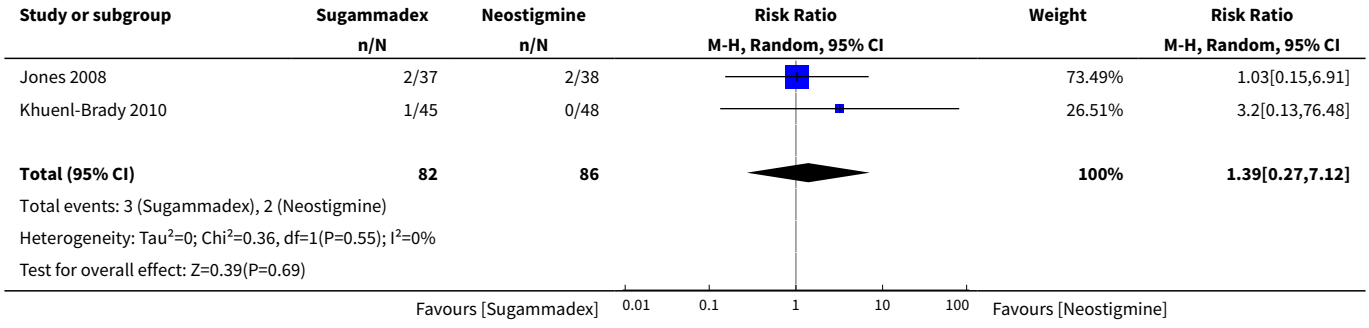




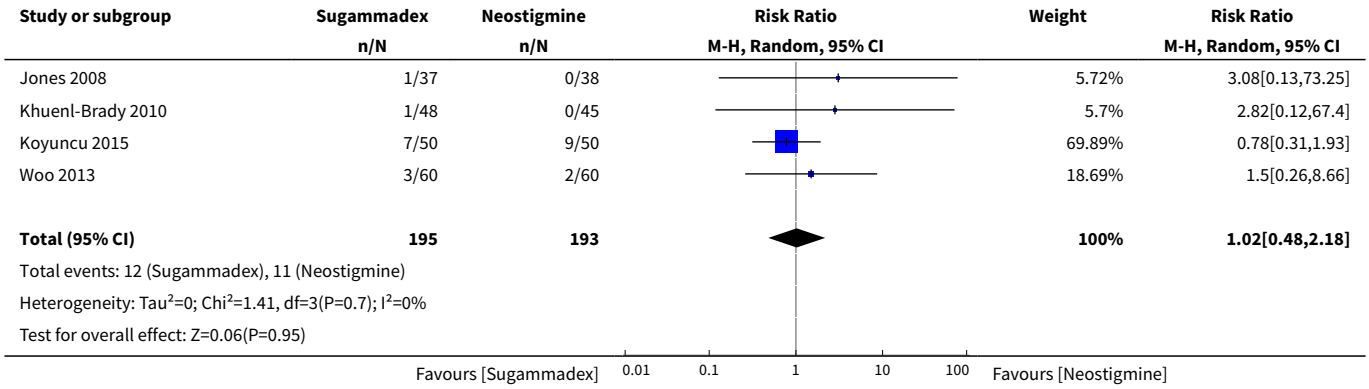
Analysis 3.14. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 14 Vomiting.



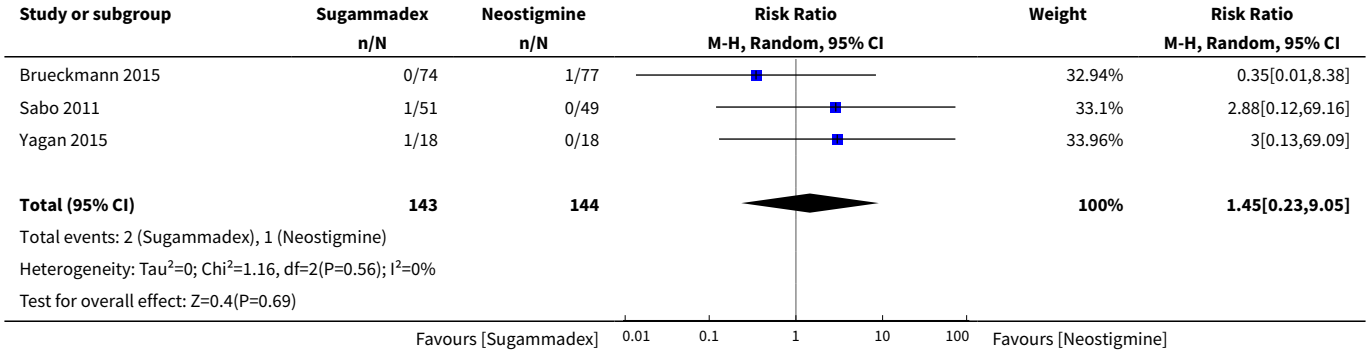
Analysis 3.15. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 15 Postprocedural nausea.



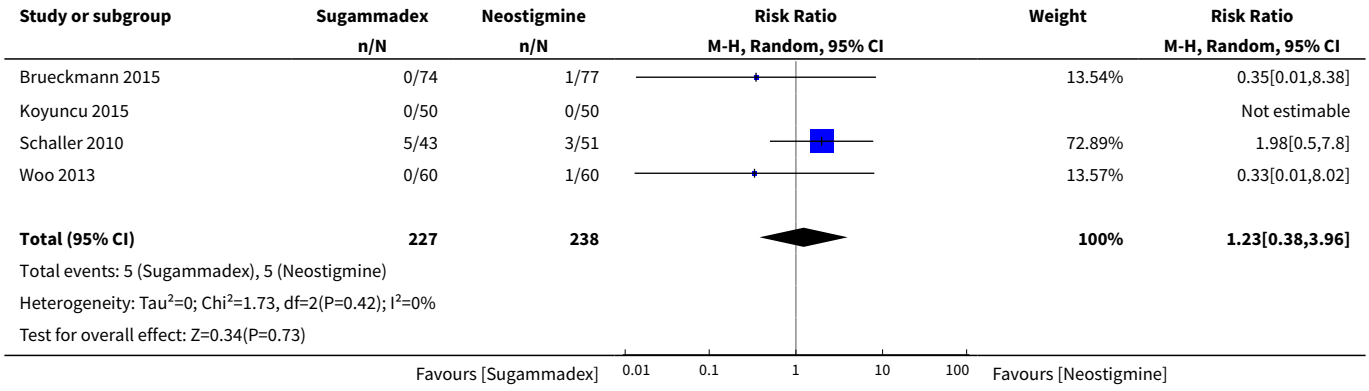
Analysis 3.16. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 16 Headache.



Analysis 3.17. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 17 Hypertension.



Analysis 3.18. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 18 Hypotension.



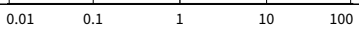
Analysis 3.19. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 19 Cough.

Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Hakimoglu 2016	5/30	5/30		36.44%	1[0.32,3.1]
Koyuncu 2015	9/50	1/50		21.5%	9[1.18,68.42]
Mekawy 2012	6/20	8/20		42.06%	0.75[0.32,1.77]
Total (95% CI)	**100**	**100**		**100%**	**1.42[0.42,4.81]**
Total events: 20 (Sugammadex), 14 (Neostigmine)					
Heterogeneity: Tau^2=0.73; Chi^2=5.71, df=2(P=0.06); I^2=64.98%					
Test for overall effect: Z=0.56(P=0.57)					

Favours [Sugammadex] Favours [Neostigmine]

Analysis 3.20. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 20 Dry mouth.

Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Blobner 2010	3/48	3/48		58.01%	1[0.21,4.71]
Khuenl-Brady 2010	0/48	4/45		21.73%	0.1[0.01,1.88]
Koyuncu 2015	0/50	2/50		20.26%	0.2[0.01,4.06]
Total (95% CI)	**146**	**143**		**100%**	**0.44[0.1,1.87]**
Total events: 3 (Sugammadex), 9 (Neostigmine)					
Heterogeneity: Tau^2=0.31; Chi^2=2.4, df=2(P=0.3); I^2=16.54%					
Test for overall effect: Z=1.11(P=0.27)					



Favours [Sugammadex] Favours [Neostigmine]

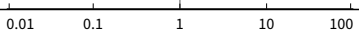
Analysis 3.21. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 21 Dizziness.

Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Jones 2008	0/37	1/38		50.09%	0.34[0.01,8.14]
Khuenl-Brady 2010	1/48	0/45		49.91%	2.82[0.12,67.4]
Total (95% CI)	**85**	**83**		**100%**	**0.98[0.1,9.23]**
Total events: 1 (Sugammadex), 1 (Neostigmine)					
Heterogeneity: Tau^2=0; Chi^2=0.85, df=1(P=0.36); I^2=0%					
Test for overall effect: Z=0.02(P=0.99)					

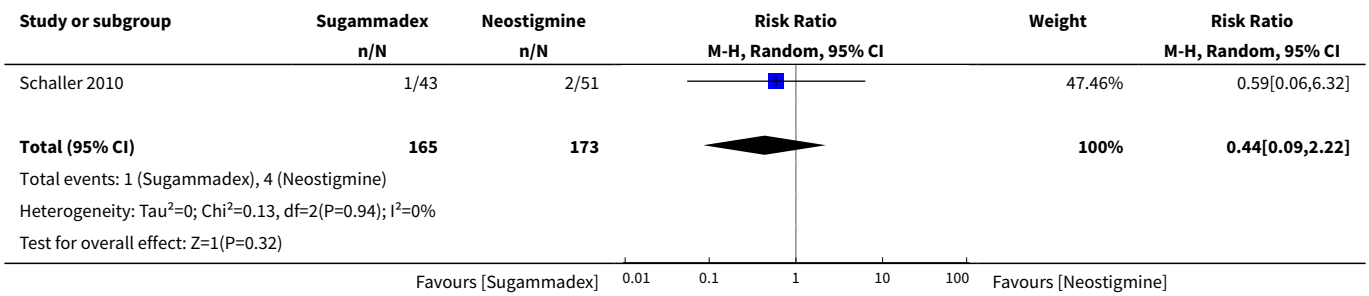
Favours [Sugammadex] Favours [Neostigmine]

Analysis 3.22. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 22 Tachycardia.

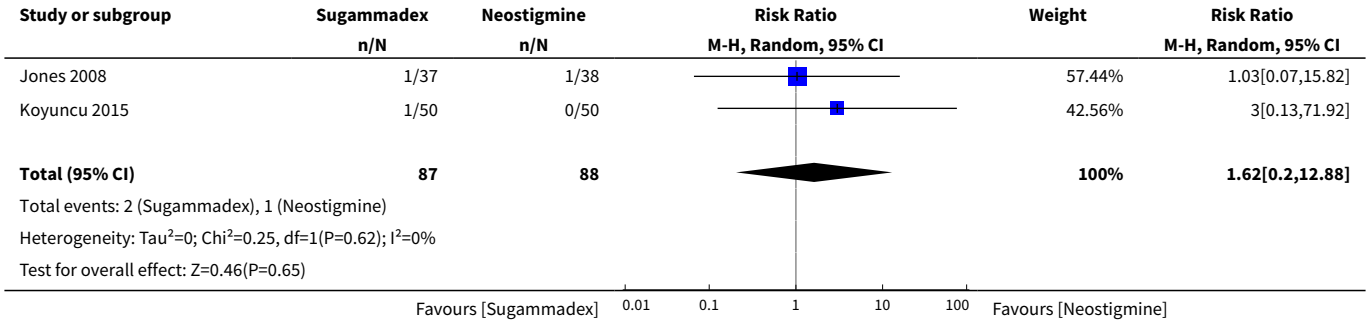
Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Brueckmann 2015	0/74	1/77		26.19%	0.35[0.01,8.38]
Khuenl-Brady 2010	0/48	1/45		26.35%	0.31[0.01,7.49]



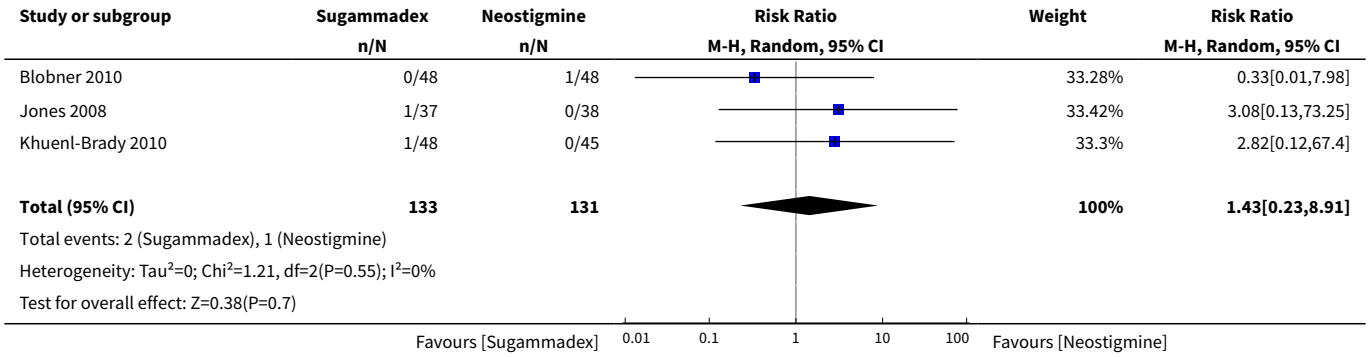
Favours [Sugammadex] Favours [Neostigmine]



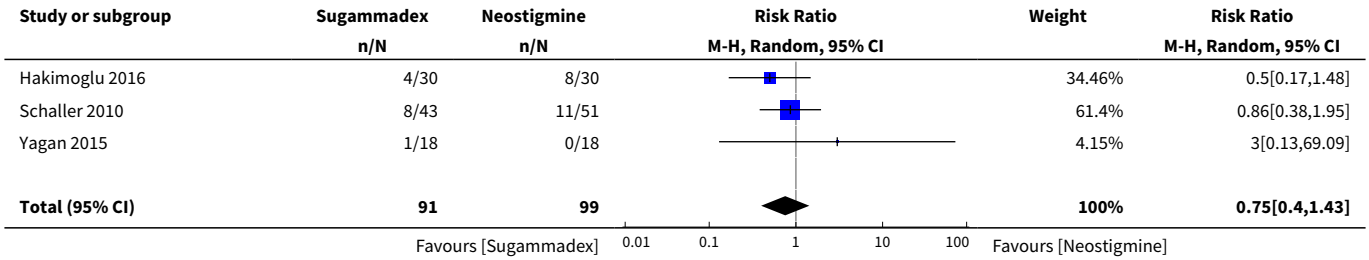
Analysis 3.23. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 23 Pruritus.

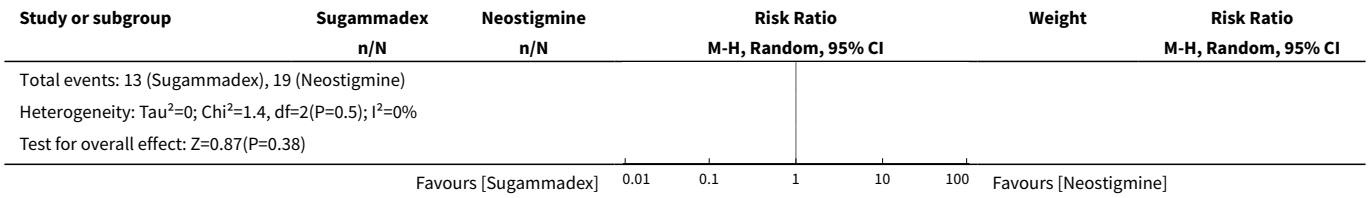


Analysis 3.24. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 24 Pyrexia.

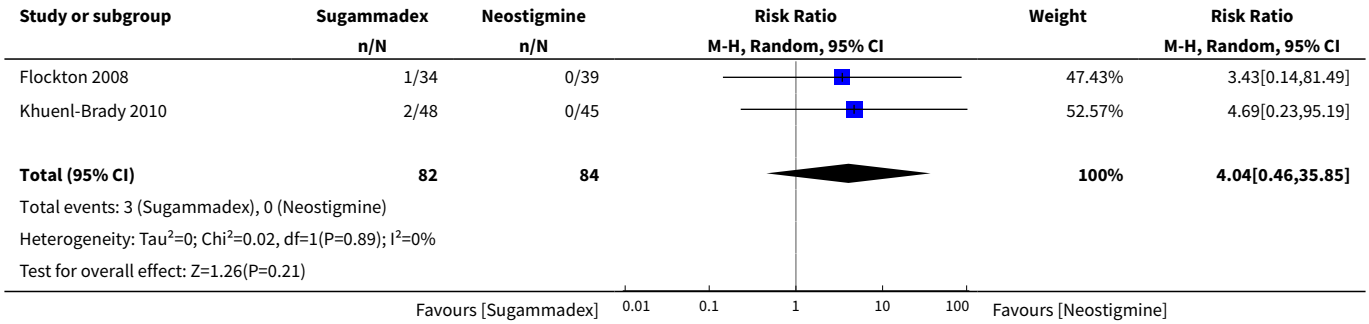


Analysis 3.25. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 25 Shivering.

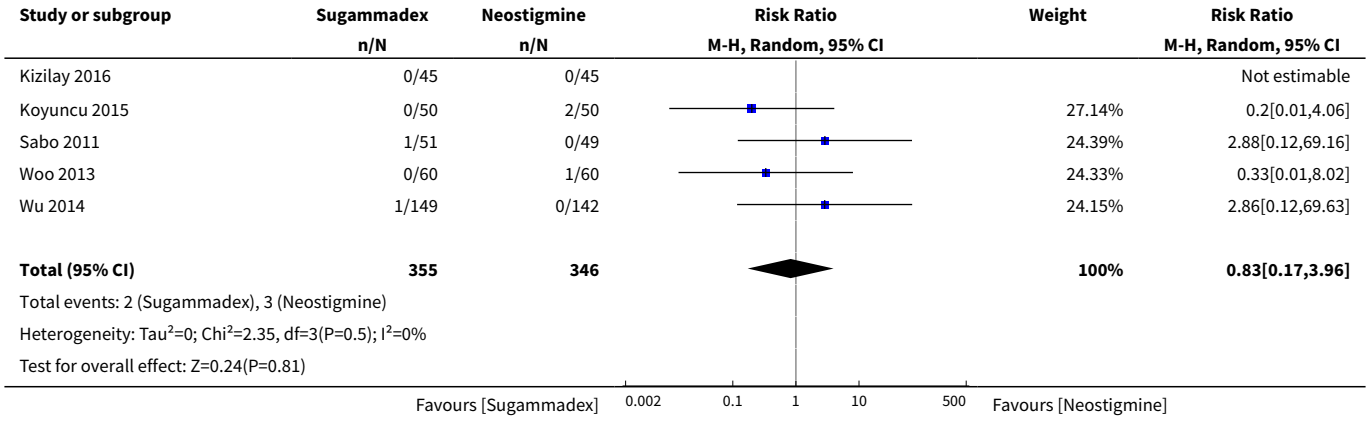




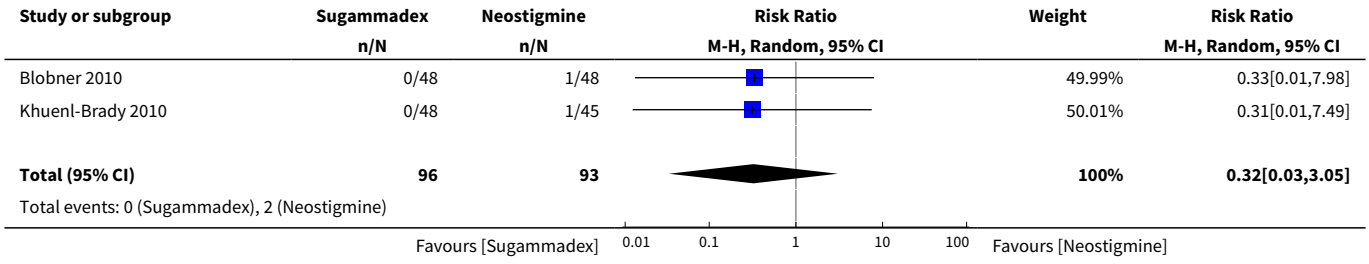
Analysis 3.26. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 26 Chills.



Analysis 3.27. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 27 Rash.



Analysis 3.28. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 28 Supraventricular extrasystoles.



Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.98); I²=0%					
Test for overall effect: Z=0.99(P=0.32)					

Favours [Sugammadex] 0.01 0.1 1 10 100 Favours [Neostigmine]

Analysis 3.29. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 29 Laryngospasm.

Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Hakimoglu 2016	1/30	4/30		54.19%	0.25[0.03,2.11]
Mekawy 2012	1/20	2/20		45.81%	0.5[0.05,5.08]
Total (95% CI)	**50**	**50**		**100%**	**0.34[0.07,1.65]**
Total events: 2 (Sugammadex), 6 (Neostigmine)					
Heterogeneity: Tau²=0; Chi²=0.19, df=1(P=0.67); I²=0%					
Test for overall effect: Z=1.33(P=0.18)					

Favours [Sugammadex] 0.01 0.1 1 10 100 Favours [Neostigmine]

Analysis 3.30. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 30 Increased upper airway secretion.

Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Brueckmann 2015	0/74	1/77		20.63%	0.35[0.01,8.38]
Wu 2014	2/149	5/142		79.37%	0.38[0.08,1.93]
Total (95% CI)	**223**	**219**		**100%**	**0.37[0.09,1.59]**
Total events: 2 (Sugammadex), 6 (Neostigmine)					
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.96); I²=0%					
Test for overall effect: Z=1.33(P=0.18)					

Favours [Sugammadex] 0.01 0.1 1 10 100 Favours [Neostigmine]

Analysis 3.31. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 31 Procedural hypertension.

Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Blobner 2010	2/48	0/48		28.41%	5[0.25,101.48]
Jones 2008	0/37	1/38		25.63%	0.34[0.01,8.14]
Khuenl-Brady 2010	2/48	1/48		45.96%	2[0.19,21.33]
Total (95% CI)	**133**	**134**		**100%**	**1.65[0.33,8.21]**
Total events: 4 (Sugammadex), 2 (Neostigmine)					
Heterogeneity: Tau²=0; Chi²=1.49, df=2(P=0.47); I²=0%					
Test for overall effect: Z=0.61(P=0.54)					

Favours [Sugammadex] 0.01 0.1 1 10 100 Favours [Neostigmine]

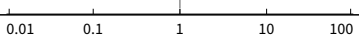
Analysis 3.32. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 32 Procedural hypotension.

Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Sabo 2011	1/51	0/49		47.83%	2.88[0.12,69.16]
Wu 2014	0/120	0/111			Not estimable
Wu 2014	0/29	5/31		52.17%	0.1[0.01,1.68]
Total (95% CI)	**200**	**191**		**100%**	**0.49[0.02,14.15]**
Total events: 1 (Sugammadex), 5 (Neostigmine)					
Heterogeneity: Tau^2=3.52; Chi^2=2.48, df=1(P=0.12); I^2=59.72%					
Test for overall effect: Z=0.41(P=0.68)					

Favours [Sugammadex] Favours [Neostigmine]

Analysis 3.33. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 33 Abdominal pain.

Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Blobner 2010	1/48	0/48		50.02%	3[0.13,71.85]
Sabo 2011	0/51	1/49		49.98%	0.32[0.01,7.68]
Total (95% CI)	**99**	**97**		**100%**	**0.98[0.1,9.27]**
Total events: 1 (Sugammadex), 1 (Neostigmine)					
Heterogeneity: Tau^2=0; Chi^2=0.95, df=1(P=0.33); I^2=0%					
Test for overall effect: Z=0.02(P=0.99)					



Favours [Sugammadex] Favours [Neostigmine]

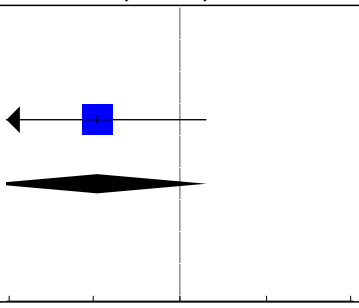
Analysis 3.34. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 34 Clinical signs of residual NMB.

Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adamus 2011	0/11	0/10			Not estimable
Balaka 2011	0/20	0/20			Not estimable
Blobner 2010	0/48	0/48			Not estimable
Cheong 2015	0/60	0/30			Not estimable
Jones 2008	0/37	0/38			Not estimable
Koc 2015	0/16	0/17			Not estimable
Wu 2014	0/149	0/142			Not estimable
Total (95% CI)	**341**	**305**			**Not estimable**
Total events: 0 (Sugammadex), 0 (Neostigmine)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours [Sugammadex] Favours [Neostigmine]

Analysis 3.35. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 35 Clinical signs of inadequate reversal of NMB.

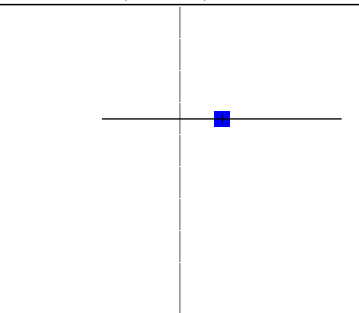
Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Flockton 2008	0/34	0/39			Not estimable
Khuenl-Brady 2010	0/48	0/45			Not estimable
Lemmens 2010	0/46	0/36			Not estimable
Woo 2013	0/60	4/60		100%	0.11[0.01,2.02]
Total (95% CI)	**188**	**180**		**100%**	**0.11[0.01,2.02]**
Total events: 0 (Sugammadex), 4 (Neostigmine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.48(P=0.14)					



Favours [Sugammadex] Favours [Neostigmine]

Analysis 3.36. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 36 Clinical signs of recurrence of residual NMB.

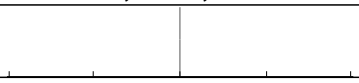
Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adamus 2011	0/11	0/10			Not estimable
Blobner 2010	0/48	0/48			Not estimable
Flockton 2008	0/34	0/39			Not estimable
Geldner 2012	1/66	0/67		48.19%	3.04[0.13,73.42]
Jones 2008	0/37	0/38			Not estimable
Kaufhold 2016	0/45	0/45			Not estimable
Khuenl-Brady 2010	0/48	0/45			Not estimable
Lemmens 2010	0/46	0/36			Not estimable
Mekawy 2012	0/20	0/20			Not estimable
Pongracz 2013	0/59	0/16			Not estimable
Sabo 2011	0/51	0/49			Not estimable
Woo 2013	0/60	2/60		51.81%	0.2[0.01,4.08]
Wu 2014	0/149	0/142			Not estimable
Total (95% CI)	**674**	**615**		**100%**	**0.74[0.05,10.74]**
Total events: 1 (Sugammadex), 2 (Neostigmine)					
Heterogeneity: Tau^2=1.22; Chi^2=1.49, df=1(P=0.22); I^2=32.72%					
Test for overall effect: Z=0.22(P=0.83)					



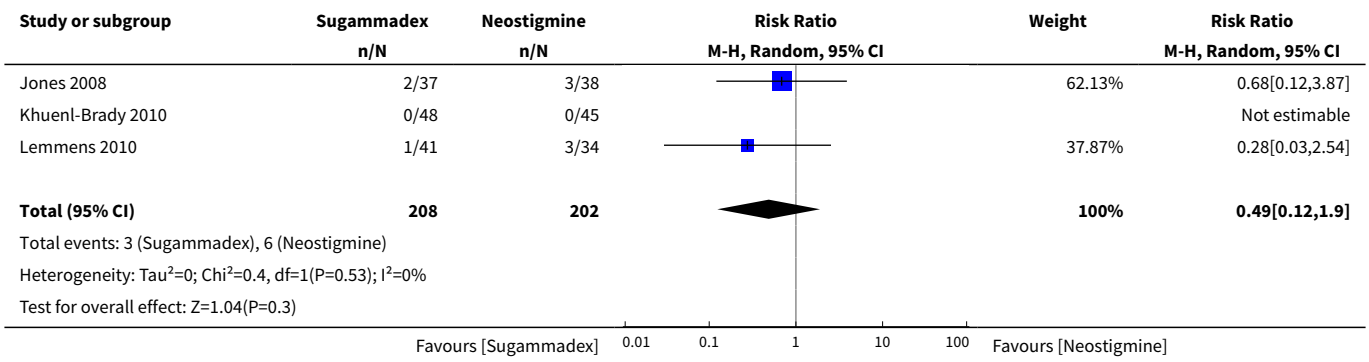
Favours [Sugammadex] Favours [Neostigmine]

Analysis 3.37. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 37 General muscle weakness at PACU discharge.

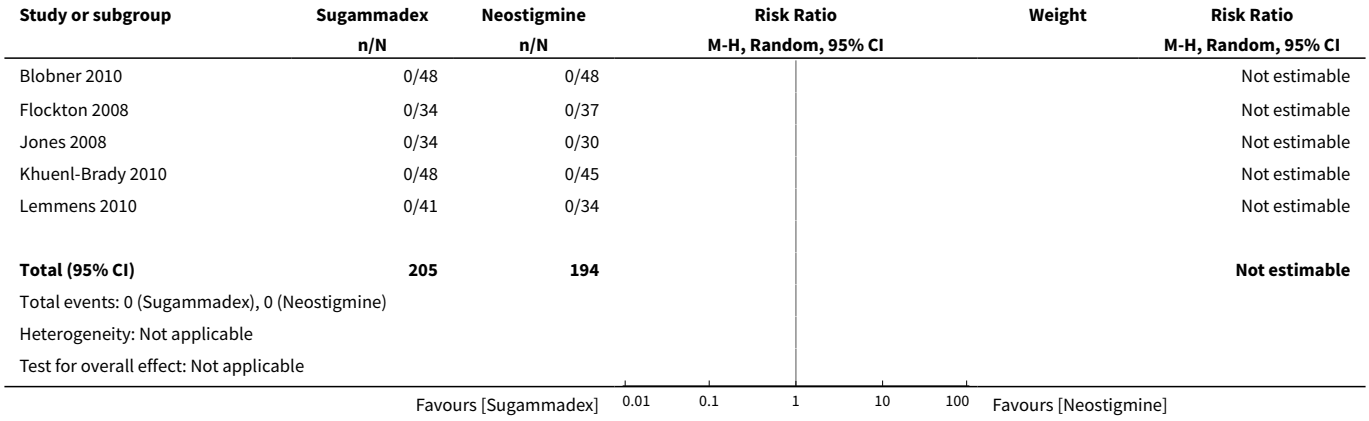
Study or subgroup	Sugammadex n/N	Neostigmine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Blobner 2010	0/48	0/48			Not estimable
Flockton 2008	0/34	0/37			Not estimable



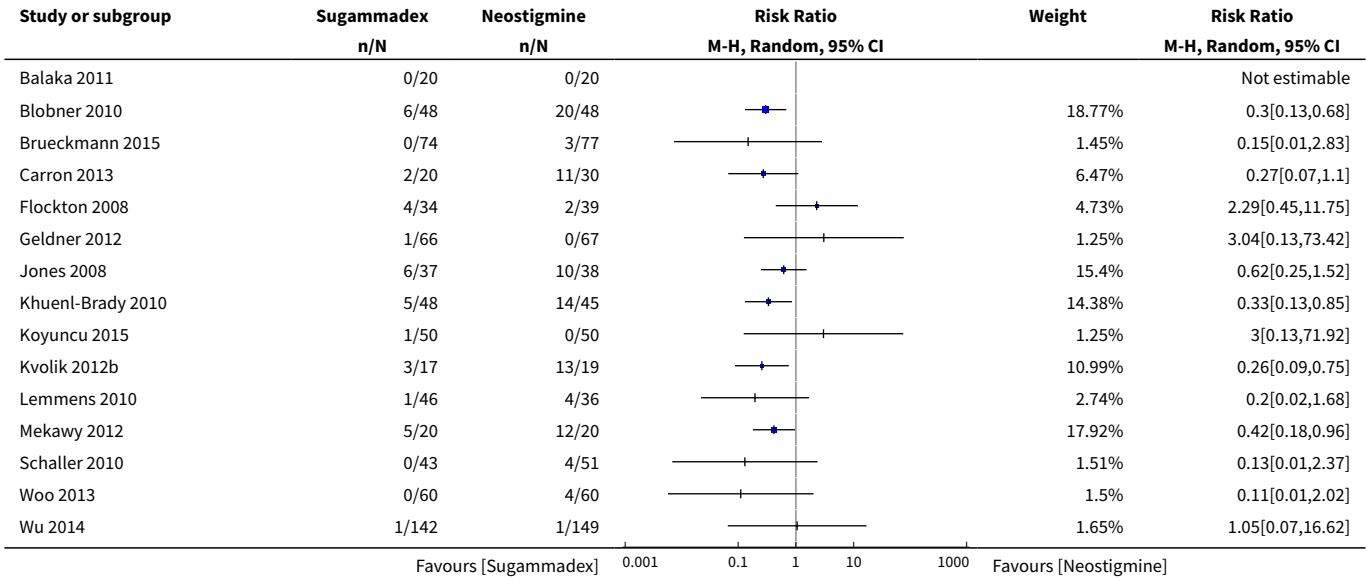
Favours [Sugammadex] Favours [Neostigmine]

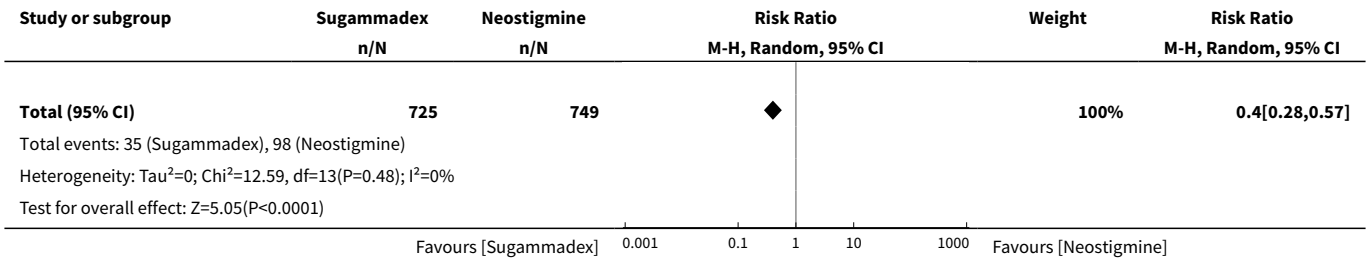


Analysis 3.38. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 38 Not able to perform 5 second head-lift at PACU discharge.

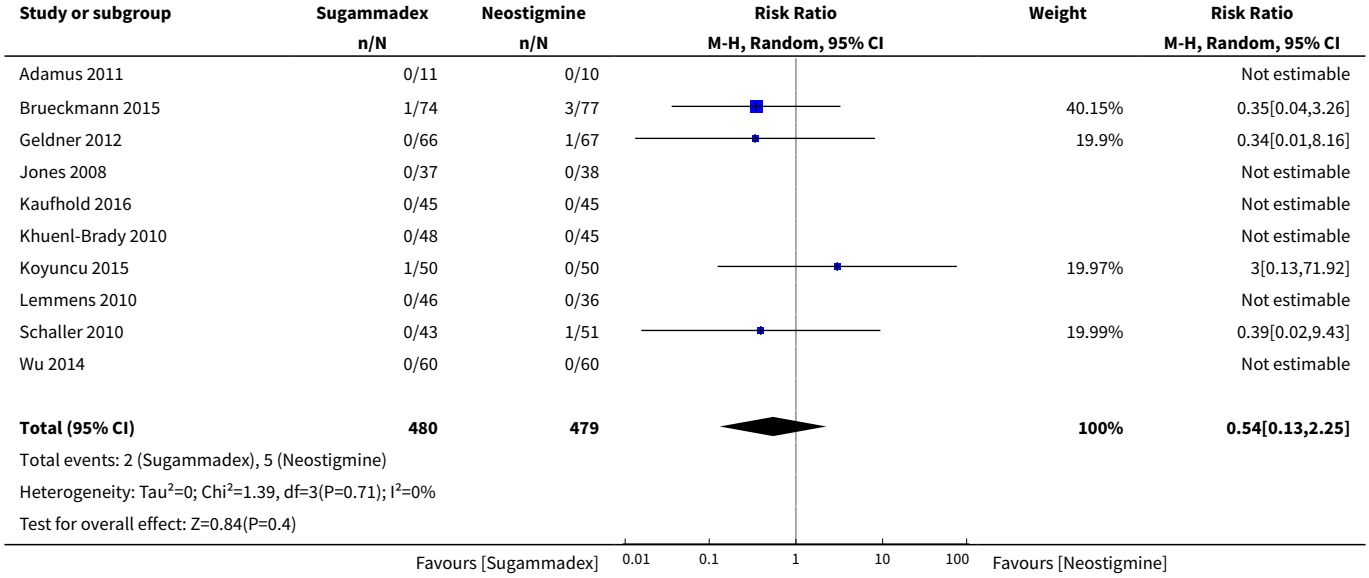


Analysis 3.39. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 39 Overall signs of postoperative residual paralysis.

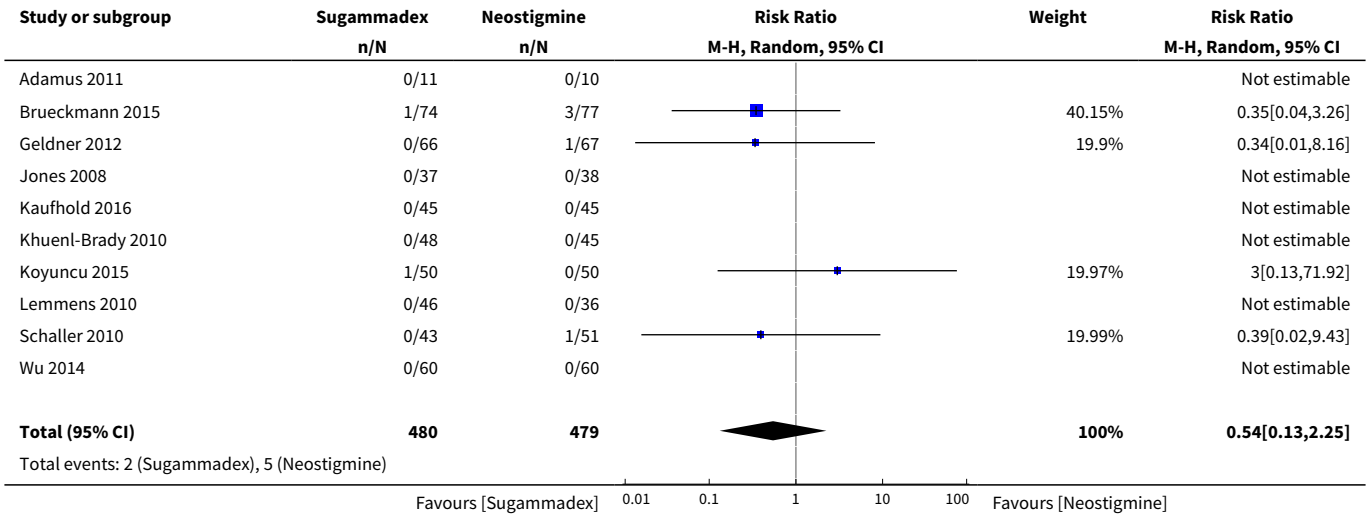


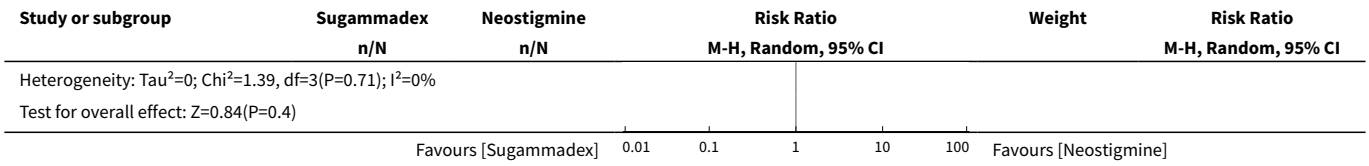


Analysis 3.40. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 40 Risk of composite serious adverse events.



Analysis 3.41. Comparison 3 Sugammadex (any dose) vs neostigmine (any dose), Outcome 41 Participants with ≥ 1 serious adverse event.





ADDITIONAL TABLES

Table 1. Table of studies ineligible for meta-analysis

Study ID	Reasons for ineligibility	Comparisons	Conclusions
Isik 2016	Primary endpoint: acute effects of sugammadex and neostigmine on renal function	Sugammadex 4 mg /kg at reappearance of PTC 1 to 2 or T2 vs neostigmine 40 µg/kg + atropine 10 µg/kg at reappearance of T2	We believe that the use of more specific and sensitive new-generation markers such as Cystatin C to evaluate kidney function will provide better understanding and interpretation of our results. Sugammadex has more tolerable effects on kidney function than does neostigmine. However, when compared with preoperative values, negative alteration of postoperative values can be seen. Neostigmine and sugammadex do not cause renal failure but may affect kidney function
Kvolik 2012a	TOFR recovery data available only as mean, no data on standard deviation, study author has not replied	Sugammadex 2 mg/kg vs neostigmine 50 µg/kg	Recovery of cough reflexes was faster and respiration more efficient in patients receiving sugammadex. Safe extubation was determined by age, TOFR recovery, and effects of other anaesthetics
Kvolik 2013	TOFR recovery data available only as mean, no data on standard deviation, study author has not replied	Sugammadex 2 mg/kg vs neostigmine 50 µg/kg + atropine 25 µg/kg	An increase in BIS Index registered after reversal of rocuronium effects was faster during the recovery period in patients who were given sugammadex as compared with neostigmine. Although rapid increase in BIS Indices was registered in sugammadex group, more sensitive measurements are needed to confirm clinical value of this observation
Martini 2014	Primary endpoint: influence of depth of the NMB on SRS (surgical rating score)	Neostigmine 1 to 2 mg + atropine 0.5 to 1 mg (for reversal of moderate NMB) vs sugammadex 4 mg/kg (for reversal of deep NMB)	Application of 5-point SRS showed that deep NMB results in improved quality of surgical conditions compared with moderate block in retroperitoneal laparoscopy, without compromise to patients' perioperative and postoperative cardiorespiratory conditions
Rahe-Meyer 2014	Comparison: sugammadex 4 mg/kg vs usual care (neostigmine with glycopyrrolate or atropine, or placebo/spontaneous recovery). Study author has not replied with separate data on neostigmine with glycopyrrolate or atropine or placebo/spontaneous recovery.	Sugammadex 4 mg/kg vs usual care (neostigmine with glycopyrrolate or atropine, or placebo/spontaneous recovery)	Sugammadex produced limited, transient (< 1 hour) increases in activated partial thromboplastin time and prothrombin time but was not associated with increased risk of bleeding vs usual care

Table 1. Table of studies ineligible for meta-analysis *(Continued)*

Raziel 2013	No useable data available for quantitative meta-analysis on recovery time or risk of adverse events	Sugammadex 2 mg/kg vs neostigmine 50 µg/kg + atropine 10 µg/kg	Sugammadex facilitates reversal of neuromuscular blockade after bariatric surgery, depending on the depth of neuromuscular blockade induced
Riga 2014	Primary outcome: cognitive function assessed by change in Mini-Mental State Evaluation test (MMSE), Clock Drawing Test, and Isaacs Set Test, performed preoperatively, 1 hour postoperatively, and at discharge (1 to 15 days postoperatively)	Sugammadex vs neostigmine/atropine	No significant difference was observed regarding cognitive function after neostigmine/atropine combination or sugammadex was received for reversal of rocuronium-induced neuromuscular blockade for elective surgery
Sherman 2014	Primary outcome: postoperative complications, data not available in useful format	Sugammadex 2 mg/kg vs neostigmine 2.5 mg/kg	Use of sugammadex (compared with neostigmine) as reversal agent following laparoscopic sleeve gastrectomy; surgery was associated with higher postoperative oxygen saturation despite lower TOF count before administration of reversal agent. Lack of differences in other measured variables may stem from the small size of patient groups studied
Sustic 2012	Outcome: gastric emptying evaluated by paracetamol absorption test	Sugammadex 2 mg/kg vs neostigmine 40 µg/kg + atropine group 15 µg/kg	Although study results show a tendency toward faster gastric emptying in sugammadex group, this difference is not significant in most, possibly owing to small sample size in this study
Tas 2015	Aim: to evaluate effects of sugammadex on postoperative nausea-vomiting, pain, coagulation parameters, and quantity of postoperative bleeding. Data not available in useful format	Neostigmine 0.05 mg/kg + atropine 0.02 mg/kg vs sugammadex 2 mg/kg	Sugammadex was associated with greater postoperative bleeding than neostigmine in septoplasty patients. For surgical procedures with high risk of bleeding, the safety of sugammadex needs to be verified

Acronyms:
BIS - Bispectral Index
MMSE - Mini-Mental State Examination
NMB - neuromuscular blockade
T2 - second twitch in train-of-four stimulation
TOFR - train-of-four ratio
PTC - post-tetanic count
SRS - surgical rating score

Table 2. Quality variables of neuromuscular monitoring methods among included trials

Study ID	Method of recording	Monitor site	Arm fixation	Supramaximal stimulation	Temperature maintained and recorded	Initial signal stabilization	Twich height calibration	Preload used
Adamus 2011	Acceleromyography	N. ulnaris, M. adductor pollicis	Yes	Yes	Yes	Not mentioned	Yes	Not mentioned
Blobner 2010	Acceleromyography	N. ulnaris, M. adductor pollicis	Yes	Yes	Yes	Not mentioned	Yes	Not mentioned
Brueckmann 2015	Acceleromyography	N. ulnaris, M. adductor pollicis	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Yes	Not mentioned
Carron 2013	Acceleromyography	N. ulnaris, M. adductor pollicis	Yes	Not mentioned	Not mentioned	Yes	Yes	No
Castro 2014	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Cheong 2015	Acceleromyography	N. ulnaris, M. adductor pollicis	Not mentioned	Not mentioned	Yes	Not mentioned	Not mentioned	Not mentioned
Flockton 2008	Acceleromyography	N. ulnaris, M. adductor pollicis	Not mentioned	Yes	Yes	Yes	Yes	Not mentioned
Gaszynski 2011	Acceleromyography	N. ulnaris, M. adductor pollicis	Yes	Yes	Yes	Not mentioned	Not mentioned	Not mentioned
Geldner 2012	Acceleromyography	N. ulnaris, M. adductor pollicis	Not mentioned	Not mentioned	Not mentioned	Yes	Yes	Not mentioned
Hakimoglu 2016	Acceleromyography	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Illman 2011	Acceleromyography	N. ulnaris,	Yes	Yes	Yes		Yes	No

Table 2. Quality variables of neuromuscular monitoring methods among included trials *(Continued)*

		M. adductor pollicis						
Isik 2016	Acceleromyography	N. ulnaris, M. adductor pollicis	Yes	Not mentioned	Yes	Not mentioned	Not mentioned	Not mentioned
Jones 2008	Acceleromyography	N. ulnaris, M. adductor pollicis	Not mentioned	Yes	Yes	Yes	Yes	Not mentioned
Kaufhold 2016	Acceleromyography	N. ulnaris, M. adductor pollicis	Yes	Yes	Yes	Yes	Yes	Not mentioned
Khuenl-Brady 2010	Acceleromyography	N. ulnaris, M. adductor pollicis	Not mentioned	Not mentioned	Yes	Yes	Yes	Not mentioned
Kizilay 2016	Acceleromyography	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Koc 2015	Acceleromyography	N. ulnaris, M. adductor pollicis	Not mentioned	Not mentioned	Yes	Not mentioned	Yes	Not mentioned
Koyuncu 2015	Acceleromyography	N. ulnaris, M. adductor pollicis	No	Yes	No	No	Yes	Not mentioned
Lemmens 2010	Acceleromyography	N. ulnaris, M. adductor pollicis	Not mentioned	Yes	Yes	Yes	Yes	Not mentioned
Martini 2014	Acceleromyography	N. ulnaris, M. adductor pollicis	Not mentioned	Yes	Not mentioned	Yes	Yes	Yes
Mekawy 2012	Acceleromyography	N. ulnaris, M. adductor pollicis	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Yes	Not mentioned
Pongracz 2013	Acceleromyography	N. ulnaris, M. adductor pollicis	Yes	Yes	Yes	Yes	Yes	Yes

Table 2. Quality variables of neuromuscular monitoring methods among included trials *(Continued)*

Sabo 2011	Acceleromyography	N. ulnaris, M. adductor pollicis	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Schaller 2010	Acceleromyography	N. ulnaris, M. adductor pollicis	Yes	Yes	Yes	Yes	Yes	Not mentioned
Tas 2015	Acceleromyography	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Woo 2013	Acceleromyography	N. ulnaris, M. adductor pollicis	Yes *	No *	Yes *	Yes	Yes	No *
Wu 2014	Acceleromyography	N. ulnaris, M. adductor pollicis	Not mentioned	Yes	Not mentioned	Yes	Yes	Not mentioned
Yagan 2015	Acceleromyography	N. ulnaris, M. adductor pollicis	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned

Studies with only abstracts were not included in this table because they did not document information regarding neuromuscular monitoring
List of abbreviations:
N. ulnaris - ulnar nerve
M. adductor pollicis - adductor pollicis muscle

Table 3. Table of adverse events

	Sugammadex			Neostigmine					
Specific adverse events	**Number of AEs**	**Number of participants**	**Risk of AEs, %**	**Number of AEs**	**Number of participants**	**Risk of AEs, %**	**RR (95% CI)**	**Number of studies**	**Total number of participants**
Cough	20	100	20,0	14	100	14,0	1.42 (0.42-4.81)	3	200
Shivering	13	91	14,3	19	99	19,2	0.75 (0.40-1.43)	3	190
Desaturation	2	63	3,2	11	71	15,5	0.23 (0.06-0.83)	2	134

Table 3. Table of adverse events *(Continued)*

General muscle weakness after extubation	13	142	9,2	22	146	15,1	0.61 (0.31-1.18)	4	288
Breath-hold	3	30	10,0	4	30	13,3	-	1	60
PONV	13	206	6,3	24	183	13,1	0.52 (0.28-0.97)	6	389
Laryngospasm	2	50	4,0	6	50	12,0	0.34 (0.07-1.65)	2	100
Not able to perform 5 second head-lift after extubation	7	193	3,6	23	202	11,4	0.34 (0.15-0.78)	6	395
Bradycardia	4	621	0,6	50	597	8,4	0.16 (0.07-0.34)	11	1218
Procedural complications	0	85	0,0	7	83	8,4	0.12 (0.02-0.97)	2	168
Postprocedural nausea	8	128	6,3	5	122	4,1	1.34 (0.47-3.81)	3	250
Dry mouth	3	146	2,1	9	143	6,3	0.44 (0.10-1.87)	3	289
Headache	12	195	6,2	11	193	5,7	1.02 (0.48-2.18)	4	388
Increased beta-N-acetyl-D-glucosaminidase	2	34	5,9	0	39	0,0	-	1	73
Strange taste in mouth	2	35	5,7	0	35	0,0	-	1	70
Nausea	17	364	4,7	20	355	5,6	0.83 (0.44-1.56)	9	719
Leukocytosis	1	46	2,2	2	36	5,6	-	1	82
Albumin present in the urine	0	48	0,0	2	48	4,2	-	1	96
Vomiting	6	149	4,0	2	148	1,4	2.05 (0.50-8.48)	4	297
Bronchospasm	2	50	4,0	1	50	2,0	-	1	100
Chills	3	82	3,7	0	84	0,0	4.04 (0.46-35.85)	2	166
General muscle weakness at PACU discharge	3	208	1,4	6	202	3,0	0.49 (0.12-1.90)	5	410

Table 3. Table of adverse events *(Continued)*

Procedural hypertension	4	133	3,0	2	134	1,5	1.65 (0.33-8.21)	3	267
Tremor	1	34	2,9	0	39	0,0	-	1	73
Altered facial sensation	1	34	2,9	0	39	0,0	-	1	73
Postprocedural hypertension	1	37	2,7	0	38	0,0	-	1	75
Paraesthesia	1	37	2,7	0	38	0,0	-	1	75
Increased blood PK	1	37	2,7	0	38	0,0	-	1	75
Increased upper airway secretions	2	223	0,9	6	219	2,7	0.37 (0.09-1.59)	2	442
Hyperhidrosis	0	37	0	1	38	2,6	-	1	75
Decreased blood protein	0	37	0	1	38	2,6	-	1	75
Restlessness	0	37	0	1	38	2,6	-	1	75
Chest discomfort	0	37	0	1	38	2,6	-	1	75
Incision site complication	0	37	0	1	38	2,6	-	1	75
Procedural hypotension	1	200	0,5	5	191	2,6	0.49 (0.02-14.1)	2	391
Postprocedural complication	0	37	0,0	1	38	2,6	-	1	75
Tachycardia	1	165	0,6	4	173	2,3	0.44 (0.09-2.22)	3	338
Pruritus	2	87	2,3	1	88	1,1	1.62 (0.20-12.88)	2	175
Intraoperative movement	1	43	2,3	1	51	2,0	-	1	94
Anxiety	0	46	0	1	46	2,2	-	1	92
Depression	0	46	0	1	46	2,2	-	1	92
Fatigue	0	46	0	1	46	2,2	-	1	92
Hypotension	5	227	2,2	5	238	2,1	1.23 (0.38-3.96)	4	465

Table 3. Table of adverse events *(Continued)*

Supraventricular extrasystoles	0	96	0,0	2	93	2,2	0.32 (0.03-3.05)	2	189
Clinical signs of inadequate reversal of NMB	0	188	0,0	4	180	2,2	0.11 (0.01-2.02)	4	368
Leukocytosis	1	46	2,2	0	36	0,0	-	1	82
Ventricular extrasystoles	0	48	0,0	1	45	2,2	-	1	93
Sleep disorder	0	48	0,0	1	45	2,2	-	1	93
Increased gamma-glutamyl-transferase	0	48	0,0	1	45	2,2	-	1	93
Retching	1	48	2,1	0	45	0,0	-	1	93
Airway complication to anaesthesia	1	48	2,1	0	45	0,0	-	1	93
Hot flush	1	48	2,1	0	45	0,0	-	1	93
Abdominal pain	1	48	2,1	0	48	0,0	-	1	96
Severe abdominal pain	1	48	2,1	0	48	0,0	-	1	96
Pharyngolaryngeal pain	1	48	2,1	0	48	0,0	-	1	96
Diarrhoea	1	48	2,1	0	48	0,0	-	1	96
Tinnitus	1	48	2,1	0	48	0,0	-	1	96
Involontary muscle contractions	0	48	0,0	1	48	2,1	-	1	96
Visual accomodation disorder	0	48	0,0	1	48	2,1	-	1	96
Increased B_2-microglobulin	0	48	0,0	1	48	2,1	-	1	96
Severe bradycardia	0	48	0,0	1	48	2,1	-	1	96
Productive cough	0	48	0,0	1	48	2,1	-	1	96
Pyrexia	2	133	1,5	1	131	0,8	1.43 (0.23-8.91)	3	264
Hypertension	2	143	1,4	1	144	0,7	1.45 (0.23-9.05)	3	287

Table 3. Table of adverse events *(Continued)*

Decreased hematocrit	1	74	1,4	0	77	0,0	-	1	151
Procedural haemorrhage	1	74	1,4	0	77	0,0	-	1	151
Delayed recovery from anaesthesia	0	74	0,0	1	77	1,3	-	1	151
Respiratory distress	0	74	0,0	1	77	1,3	-	1	151
Dizziness	1	85	1,2	1	83	1,2	0.98 (0.10-9.23)	2	168
Abdominal pain	1	99	1,0	1	97	1,0	0.98 (0.10-9.27)	2	196
Rash	2	355	0,6	3	346	0,9	0.83 (0.17-3.96)	5	701
Severe muscle weakness	0	149	0,0	1	142	0,7	-	1	291
Mild hypoventilation	1	149	0,7	0	142	0,0	-	1	291
Clinical signs of recurrence of residual NMB	1	674	0,1	2	615	0,3	0.74 (0.05-10.7)	13	1289
Clinical signs of residual NMB	0	341	0,0	0	305	0,0	-	7	646
Not able to perform 5 second head-lift at PACU discharge	0	205	0,0	0	194	0,0	-	5	399
Redness at injection site	0	50	0,0	0	50	0,0	-	1	100
Hypersensitivity	0	60	0,0	0	30	0,0	-	1	90

Table of reported adverse events possibly, probably, or definitely related to sugammadex or neostigmine, listed in descending order according to risk of adverse events. Furthermore, the number of studies observing for each adverse event is presented
List of abbreviations:
NMB - neuromuscular blockade
PACU - post-anaesthesia care unit

APPENDICES

Appendix 1. MEDLINE (Ovid) 1950 to May 2017

#1 "sugammadex".mp.

#2 "selective relaxant binding agent".mp.

#3 "SRBA".mp.

#4 "org 25969".mp.

#5 "bridion".mp.

#6 or/1-5

Appendix 2. Embase (Ovid) 1980 to May 2017

#1 "sugammadex".mp.

#2 "selective relaxant binding agent".mp.

#3 "SRBA".mp.

#4 "org 25969".mp.

#5 "bridion".mp.

#6 or/1-5

Appendix 3. CENTRAL (The Cochrane Library; 2017, Issue 4)

#1 "sugammadex"

#2 "selective relaxant binding agent"

#3 "SRBA"

#4 "org 25969"

#5 "bridion"

#6 or/1-5

Appendix 4. Assessment of risk of bias in included studies

1. Random sequence generation

Assessment of selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.

Low risk **:** any truly random process based on computer-generated random numbers, random number table, coin tossing, shuffling of cards, shuffling of envelopes, throwing of dice, or drawing of lots.

High risk **:** any non-random process based on date of birth, date of admission, hospital record number, clinic record number, results of laboratory tests, or allocation by availability of the intervention, judgment of clinician, or preference of participant.

Unclear risk **:** insufficient information.

2. Allocation concealment

Assessment of allocation bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment.

Low risk: central allocation including telephone, Web-based, and pharmacy-controlled randomization, use of sequentially numbered opaque sealed envelopes (SNOSE) or sequentially numbered drug containers of identical appearance.

High risk: open random allocation schedule, assignment envelopes without appropriate safeguards, alteration or rotation, date of birth, case control number, or any other explicitly unconcealed procedure.

Unclear risk: insufficient information.

3. Blinding

Assessment of performance bias due to knowledge of allocated interventions by participants and personnel during the study.

PERFORMANCE BIAS: blinding of participants

Low risk: blinding of participants ensured and unlikely to have been broken.

High risk: no blinding or incomplete blinding of participants, and outcome likely to be influenced by lack of blinding, appropriate blinding of participants likely to have been broken or study categorized as ”open-label”.

Unclear risk*:* insufficient information.

PERFORMANCE BIAS: blinding of key personnel (anaesthesiologist and surgeon)

Low risk: blinding of key personnel ensured and unlikely to have been broken.

High risk: no blinding or incomplete blinding of key personnel and outcome likely to be influenced by lack of blinding, appropriate blinding of key personnel likely to have been broken or study categorized as ”open-label”.

Unclear risk*:* insufficient information.

DETECTION BIAS: blinding of primary outcome (TOF-watch) assessment

Low risk: blinding of TOF-watch assessor ensured and unlikely to have been broken.

High risk: no blinding or incomplete blinding of TOF-watch assessor and outcome likely to be influenced by lack of blinding, appropriate blinding of TOF-watch assessor likely to have been broken, study categorized as ”open-label”.

Unclear risk: insufficient information.

DETECTION BIAS: blinding of secondary outcome (safety) assessment

Low risk: blinding of safety assessor ensured and unlikely to have been broken.

High risk*:* no blinding or incomplete blinding of safety assessor and outcome likely to be influenced by lack of blinding, appropriate blinding of safety assessor likely to have been broken or study categorized as ”open-label”.

Unclear risk: insufficient information.

4. Incomplete outcome data

Assessment of attrition bias due to quantity, nature, or handling of incomplete outcome data.

Low risk: no missing outcome data, missing outcome data described (numbers and reasons for drop-puts and withdrawals) and balanced in numbers across intervention groups with similar reasons for missing data across groups, or missing data have been imputed by appropriate methods.

High risk: missing outcome data, missing outcome data not described (numbers and reasons for drop-puts and withdrawals) or not balanced in numbers across intervention groups with similar reasons for missing data across groups, or missing data have not been imputed by appropriate methods.

Unclear risk*:* insufficient information.

5. Selective reporting

Assesment of reporting bias due to selective outcome reporting.

Low risk: Study protocol is available, and all of the study’s prespecified (primary and secondary) outcomes of interest to the review have been reported in the prespecified way, or the study protocol is not available but it is clear that the published report includes all expected outcomes, including those that were prespecified.

High risk: Not all of the study’s prespecified primary outcomes have been reported, one or more of the primary outcomes are reported using measurements, analysis methods, or subsets of data that were not prespecified, one or more primary outcomes were not prespecified, one or more outcomes of interest to the review are reported incompletely so that they cannot be entered into the meta-analysis, or the study report fails to include results for a key outcome that would be expected to be reported in such a study.

Unclear risk*:* insufficient information.

6. Funding bias

Assesment of any possible funding bias.

Low risk: reported no funding or funding by trial authors themselves, funding from Universities and other public institutions.

High risk: funding from private investor, pharmaceutical companies, or any trial investigator employed by or receiving grants, travel funding, or honoraria from a pharmaceutical company

Unclear risk*:* insufficient information.

7. Other bias

Assessment of any possible sources of bias not addressed in domains one to six.

Low risk: Report appears to be free of bias due to problems not covered elsewhere in the table.

High risk: At least one important bias is present that is related to study design, sample size calculation, early stopping because of some data-dependent process, extreme baseline imbalance, academic bias, claimed fraudulence, or other problems.

Unclear risk*:* Information is insufficient for assessment of whether an important risk of bias exists, or the rationale or evidence is insufficient to suggest that an identified problem will introduce bias.

Appendix 5. All abbreviations

ACh - Acetylcholine

AE – Adverse event

AEs – Adverse events

aPTT - Activated partial thromboplastin time

ASA - American Society of Anaesthesiologists

AST - Aspartate aminotransferase

BIS - Bispectral Index

BMI - Body mass index

BP - Blood pressure

BUN - Blood urea nitrogen

CBW - Corrected body weight

CI – Confidence interval

CIs – Confidence intervals

CNS - Central nervous system

COPD - Chronic obstructive pulmonary disease

Cr - Creatinine

CrCL - Creatinine clearance

Cys - Cysteine

DEF – Dynamic end-tidal forcing

DL – Diffusion lung capacity

DLCO/VA – Diffusion lung capacity for carbon monoxide/alveolar volume ratio

dNMB – deep neuromuscular blockage

ECG - electrocardiography

eGFR – estimated glomerular filtration rate

EMGdi - diaphragmatic electromyogram

ENT – Ear–nose-throat

FOC - Free of charge

FEV_1 – Forced expiratory volume in one second

FVC – Functional vital capacity

GCS – Glasgow Coma Scale

GOLD – Global Initiative for Cronic Obstructive Lung Disease

GRADE – Grades of Recommendation Assessment, Development and Evaluation

H - Hour

Hb - Haemoglobin

HR - Heart rate

ICU - Intensive care unit

INR - International normalized ratio

IOP - Intraocular pressure

ITT - Intention to treat

IV - Intravenous

kg - Kilograms

LBW - Lean body weight

M^2 - Meters squared

mA - Miliamperes

MAC - Minimal alveolar concentration

MAP - Mean arterial blood pressure

MedDRA - Medical Dictionary for Regulatory Activities

MELD - Model for End-Stage Liver Disease

METS - Metabolic equivalent of tasks

MG - Myasthenia gravis

Mg - Milligrams

MHR - Mean heart rate

Min - Minutes

Mmol/L - Milimol/litre

MMSE - Mini-Mental State Examination

MO - Morbidly obese

NM - Neuromuscular

NMB - Neuromuscular blockade

NMBA - Neuromuscular blocking agent

NMBAs – Neuromuscular blocking agents

NMJ – Neuromuscular Junction

NMT - Neuromuscular technique

NNTB - Number needed to treat for an additional beneficial outcome

NS - Not significant

NSQIP - National Surgical Quality Improvement Program

NYHA - New York Heart Assosiation

PACU - Post-anaesthesia care unit

PADSS - Post-anaesthesia discharge score system

PEF - Peak expiratory flow

PONV - Postoperative nausea and vomiting

PORC - Postoperative residual curarization

PPC - Plasma paracetamol concentration

PQRS - Postoperative Quality Recovery Scale

PRSES - Postoperative Respiratory System Evaluation Score

PT - Prothrombin time

PTC - Post-tetanic count

QTc - QTc interval

RBW – Real body weight

RCT – Randomized controlled trial

RCTs – Randomized controlled trials

RPONB - Residual postoperative neuromuscular blockade

RR – Risk ratio

SAE - Serious adverse event

SAEs – Serious adverse events

SAS - SAS Institute

SD - Standard deviation

Sec - Seconds

SEVO - Sevoflurane

SO - Super obese

Sq - Square

SRS - Surgical Rating Scale

SX - Symptoms

T – Twitch in train-of-four stimulation

T2 - second twitch in train-of-four stimulation

TBW – Total body weight

TIVA – Total intravenous anaesthesia

TOF - Train of four

TOFR - Train-of-four ratio

TSA – Trial sequential analysis

TSH - Thyroid-stimulating hormone

µg - Micrograms

VAS - Visual Analogue Scale

Vs - Versus

XLIF - Extreme lateral interbody fusion

Yr - Years

WHAT'S NEW

Date	Event	Description
29 September 2017	Amended	We corrected a typo in the Plain language summary. We changed the sentence: "Participants receiving sugammadex appeared to have a 40% reduced risk of experiencing harmful events than those given *sugammadex*", to "Participants receiving sugammadex appeared to have a 40% reduced risk of experiencing harmful events than those given*n eostigmine*" in Key results under Plain language summary section.

HISTORY

Review first published: Issue 8, 2017

Date	Event	Description
10 May 2017	New citation required and conclusions have changed	The original published review (Abrishami 2009) concluded that trials found no difference in the instance of unwanted effects between sugammadex and neostigmine. Our updated review concludes that sugammadex reduces the risk of adverse events when compared with neostigmine.
10 May 2017	New search has been performed	The original published review (Abrishami 2009) has been updated by new review authors and split into two reviews, one review comparing sugammadex and neostigmine, and the other comparing sugammadex and placebo, as well as different doses of sugammadex. This review compares sugammadex and neostigmine and has been updated as of 10 May 2017 with regard to the search. The new search added eight years of research and

Date	Event	Description
		38 new trials to this review, including three trials that compared sugammadex and neostigmine. In total, this review comprises 41 included studies as well as 3 studies awaiting classification and 20 ongoing studies. Furthermore, review authors have completely revised the current review methodologically in accordance with the latest recommendations from Cochrane, with incorporation of full risk of bias tables, summary of finding tables, and trial sequential analysis. For more details, see Differences between protocol and review and Published notes.

CONTRIBUTIONS OF AUTHORS

Updated review

Ana-Marija Hristovska (AMH), Patricia Duch (PD), Mikkel Allingstrup (MA), Arash Afshari (AA).

Conceiving the review: AMH, AA, PD.

Co-ordinating the review: AMH.

Undertaking manual searches: AMH, PD; MA.

Screening search results: AMH, PD.

Organizing retrieval of papers: AMH, PD, MA.

Screening retrieved papers against inclusion criteria: AMH, PD.

Appraising quality of papers: AMH, PD, AA.

Abstracting data from papers: AMH, PD.

Writing to authors of papers for additional information: AMH.

Providing additional data about papers: AMH.

Obtaining and screening data from unpublished trials: AMH, PD.

Managing data for the review: AMH.

Entering data into Review Manager (RevMan 5.3): AMH.

Analysing RevMan statistical data: AMH.

Conducting other statistical analysis not using RevMan: AA.

Performing double entry of data (data entered by person one: AMH; data entered by person two: PD).

Interpreting data: AMH, AA.

Making statistical inferences: AA.

Writing the review: AMH (abstract, methods, results, discussion, conclusions), PD (discussion), MA (background, methods), AA (abstract, methods, results, discussion, conclusions).

Securing funding for the review: This review was not funded.

Performing previous work that was the foundation of the present study: none of the review authors.

Taking responsibility for reading and checking the review before submission: AMH, AA.

DECLARATIONS OF INTEREST

Ana-Marija Hristovska declares no conflict of interest.

Patricia Duch declares no conflict of interest.

Mikkel Allingstrup declares no conflict of interest.

Arash Afshari declares no conflict of interest.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2017

This updated review does not follow the protocol (Abrishami 2008)) prepared for the original version of this review. This is because after several discussions with the editorial team, we made the decision to split the original review (Abrishami 2009) into two reviews based on the extensive number of publications (> 70) identified by the updated search using various comparators, interventions, and outcome measures. In this updated review, we decided to focus only on sugammadex and neostigmine and to compare their efficacy and safety.

NOTES

July 2017

After several discussions with the editorial team, a decision was reached to split the original review (Abrishami 2009), into two reviews based on the very extensive number of publications (>70) identified by the updated search with various comparators, interventions and different outcome measures. This updated review therefore does not follow the protocol (Abrishami 2008) made for the original version of the review (Abrishami 2009). In the updated review, we decided to only focus on Sugammadex and Neostimgine and compare their efficacy and safety.

INDEX TERMS

Medical Subject Headings (MeSH)

*Neuromuscular Blockade; Androstanols [antagonists & inhibitors]; Atracurium [analogs & derivatives] [antagonists & inhibitors]; Cholinesterase Inhibitors [administration & dosage] [adverse effects] [*pharmacology]; Neostigmine [administration & dosage] [adverse effects] [*pharmacology]; Neuromuscular Nondepolarizing Agents [*antagonists & inhibitors]; Randomized Controlled Trials as Topic; Rocuronium; Sugammadex; Time Factors; Vecuronium Bromide [antagonists & inhibitors]; gamma-Cyclodextrins [administration & dosage] [adverse effects] [*pharmacology]

MeSH check words

Adult; Humans