https://doi.org/10.1590/1806-9282.2022D687

Sugammadex in awakening from general anesthesia: systematic review and meta-analysis

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INTRODUCTION

General anesthesia (GA) is used in surgical procedures, and it consists of the induced, reversible, and controlled loss of consciousness, which maintains the patient in a state of sedation, analgesia, amnesia, and muscle paralysis induced by neuromuscular blockers (NMBs). Although the mechanism of action of GA is not entirely clear, it is known that signals along the nerves responsible for passing stimuli are interrupted and not processed by the central nervous system after anesthetic administration. The entire anesthetic process requires protection of the airways and/or mechanical ventilation, because by causing muscle paralysis, the agents cause the inhibition of spontaneous breathing, together with uncontrolled hemodynamic processes. Some of the neuroblockers (NBs) available for use in GA are as follows:

1) *Rocuronium* – Androstanol non-depolarizing neuromuscular blocking agent (NMBA), with a mono-quaternary structure, being a weaker nicotinic antagonist than pancuronium (pancuronium bromide is a non-depolarizing long-acting neuromuscular blocking amino ester).
2) *Vecuronium bromide* – Mono-quaternary homolog of pancuronium and a non-depolarizing NMBA, with a shorter action than pancuronium, which may provide an advantage or be used as an alternative, as it does not have significant cardiovascular effects, does not depend on good renal function, and has a short duration of action and easy reversibility compared to other NB agents.
3) *Succinylcholine* – Quaternary skeletal muscle relaxant usually used in the form of bromide, chloride, or iodide. It is a depolarizing relaxant, with action in approximately 30 s and an average duration of 3–5 min, used in medical procedures when a brief period of muscle relaxation is required.
4) *Cisatracurium* – NMB, indicated as an adjunct to GA to facilitate tracheal intubation and skeletal muscle relaxation during surgical procedures or mechanical ventilation in intensive care unit (ICU) environments.

NMB should be monitored through quantitative (accelerometry, electromyography, cinematography) or qualitative measurements. The latter is performed using a peripheral nerve stimulator that determines the depth of block (TOF) considering the TOF measurement >0.9 as an indicative parameter for extubation[1] (Appendix IV).

At the end of the anesthetic process, NMB reversers are used in order to shorten the muscle activity recovery time. The drugs most frequently used for this purpose are as follows:

1) Sugammadex – A selective antagonist of steroidal NMBA (e.g., rocuronium, vecuronium, and pancuronium). It is a water-soluble substance that, by displacing the NMBA from the neuromuscular junction receptors, forms a stable compound with it, producing cessation of the NMB action in anesthesia.
2) Neostigmine – Cholinesterase inhibitor used in the treatment of myasthenia gravis and to reverse the myorelaxant effects of muscle blockers.

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on April 20, 2022. Accepted on April 20, 2022.

3) Pyridostigmine bromide— Cholinesterase inhibitor with a slightly longer duration of action than neostigmine.
4) Edrophonium – A rapid-onset, short-acting cholinesterase inhibitor used in cardiac arrhythmias and in the diagnosis of myasthenia gravis. It has also been used as an antidote to curare poisons and as a muscarinic antagonist.
5) Atropine sulfate is indicated for the temporary blocking of serious or potentially lethal muscarinic effects, for example, as an antisialogogue, an anti-vagal agent, an antidote for organophosphorus, carbamate, or muscarinic mushroom poisoning, and to treat symptomatic bradycardia.
6) Glycopyrrolate – A muscarinic antagonist used as an antispasmodic in some disorders of the gastrointestinal tract and to reduce salivation.

This study aimed to compare the efficacy and safety of *sugammadex* with other substances commonly used in the reversal of NMB in GA, such as *neostigmine* and *pyridostigmine* associated with atropine sulfate or glycopyrrolate.

METHODS

In this section, the clinical question, the structured question (PICO), eligibility criteria of the studies, sources of information consulted, search strategies used, critical evaluation method (risk of bias), quality of evidence, data extracted, measures used to express the results, and method of analysis are discussed.

Clinical question

Is there evidence of efficacy and safety in the use of sugammadex compared to neostigmine or prostigmine in reversing NMB in inhaled general anesthesia (IGA)?

Structured question

P (population): Patients undergoing GA using NMBs.
I (intervention): Reversal of the blockade using sugammadex.
C (comparison): Reversal of conventional block with neostigmine or neostigmine+atropine.
O (outcome)[1]: Time to extubation, recovery time to reach TOF 90% (0.9), nausea, vomiting, hypoxemia, hypotension, bradycardia, hypertension.

Eligibility criteria

- Components of PICO;
- Randomized clinical trials (RCTs);
- No date restriction;
- Languages: English, Spanish, and Portuguese;
- Full text or abstract with necessary data;
- Outcomes expressed in absolute number of events or mean/median with variation.

Exclusion criteria

- Observational and non-comparative studies;
- In vitro and/or animal studies;
- Case series or case reports;
- Narrative or systematic reviews.

Sources of information consulted and search strategies

Medline via PubMed, EMBASE

Search strategy: Sugammadex AND Random*

Risk of bias and quality of evidence

For the RCTs, the following risks of bias were evaluated: focal question, randomization, blindfolded allocation, double blinding, evaluator blinding, losses, analysis by intention to treat (ITT), definition of outcomes, and sample size calculation.

Data extracted

Author, year of publication, study design, characteristics and number of patients, intervention, comparison, outcomes: time to extubation, recovery time to reach TOF 90% (0.9)[1], nausea, vomiting, hypoxemia, hypotension, bradycardia, hypertension.

Outcome measures

For categorical variables, we used absolute numbers, percentage, absolute risk, risk reduction or increase, number needed to treat (NNT) or number needed to harm (NNH), and 95% confidence interval (95%CI). For continuous variables, means or difference in means (MD) with standard deviation.

Expression of the results

When there was the possibility of aggregating the results of the included studies with respect to one or more common outcomes, a meta-analysis was performed using the RevMan version 5.3 software (Cochrane)[2].

To calculate the mean and standard deviation, when not presented in the study, the software VassarStats: Website for Statistical Computation was used[3].

Analysis of the quality of evidence

The quality of the evidence was assessed using GRADEpro software[4].

RESULTS

The results are presented using flowchart (Figure 1) of study selection, summaries of RCTs (Appendix 1), risk of bias (Appendix 2), results by outcome, quality of GRADE evidence (Appendix 3), and summary of the evidence.

In total, 265 studies were retrieved (Medline via PubMed), as well as 65 from the EMBASE database. After applying the eligibility criteria and evaluating titles and abstracts, 55 studies were selected, of which 36 were included[5-40] for evaluation of the full text and inclusion in the meta-analysis, with 19 studies excluded[41-59] (Figure 1). Three studies retrieved from EMBASE (Quang[5], Lemmens[6] and Woo[7]) were also found in the Medline search via PubMed. The studies by Pişkin[8] and Yağan[9] were included only once because they were cited twice with different PMIDs.

Characteristics of the included studies

The included studies met the eligibility criteria, being all RCTs, including pediatric and adult patients, with different doses of intervention (sugammadex), compared with neostigmine with or without association, during small, medium, and large surgeries. The summary of the characteristics of the included studies can be found in Appendix 1.

Risk of bias and quality of evidence

Regarding biases, randomization was adequate in most studies; considering the blinded allocation of distribution, there was a small preponderance of studies that performed blinded allocation in relation to those that did not; double blinding and evaluator blinding either did not occur or was not informed in most studies; the losses in most studies were not significant; the prognostic features in almost all studies were reported and adequate; the outcomes, with the exception of one study, were adequate; most studies did not analyze ITT; in most studies, the sample calculation was performed; and in only two studies, there was an early interruption.

The risk of bias and the quality of evidence can be found in Appendix 2.

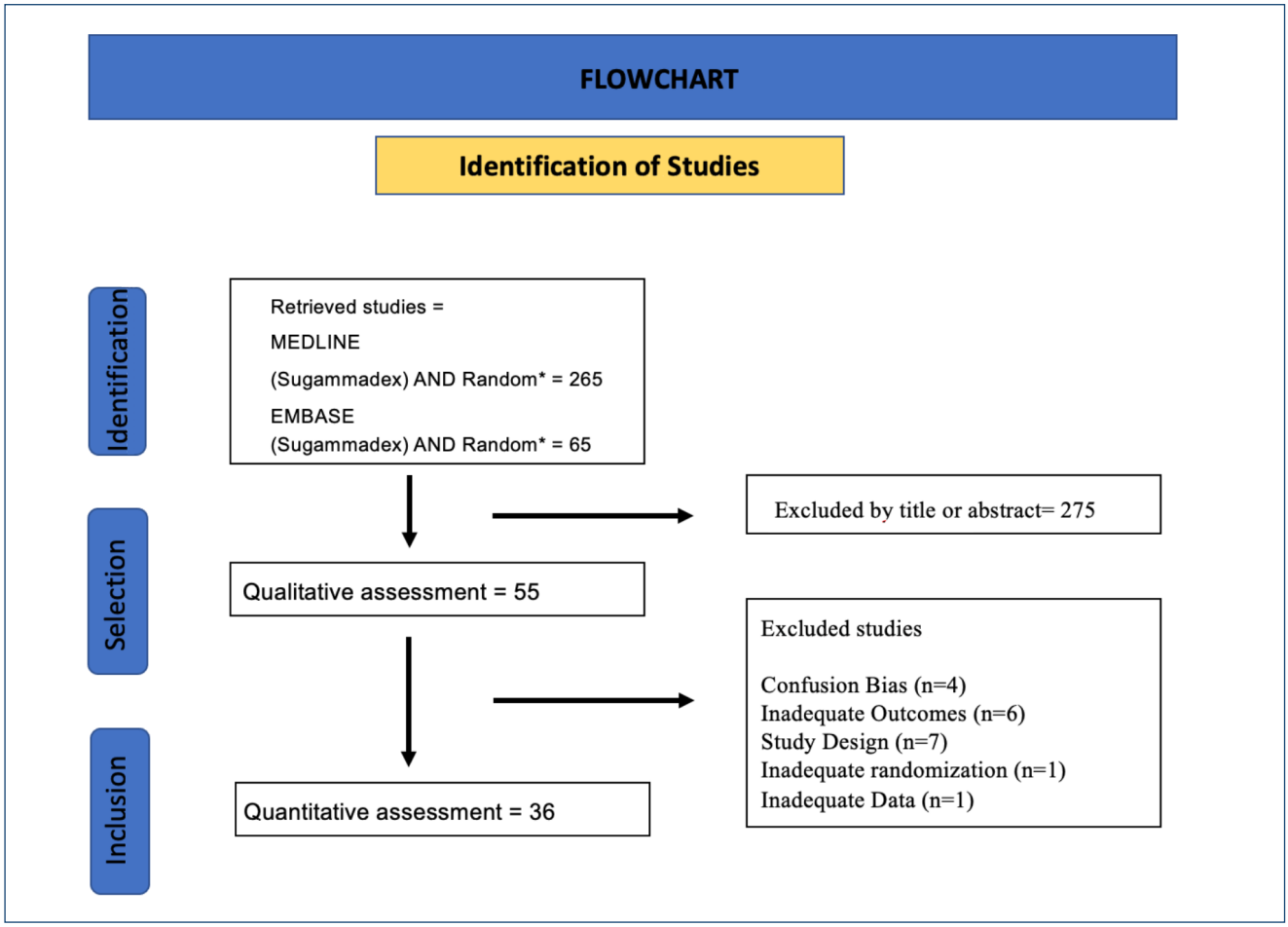

Figure 1. Flowchart of selected studies.

Analysis of results by outcome

1) Extubation time

In the evaluation of time to extubation (min), 12 studies were included, with 699 patients in the SUGAMMADEX group and 708 in the NEOSTIGMINE group.

With the drug SUGAMMADEX, extubation time was shorter compared to NEOSTIGMINE, with a significant reduction, MD= -3.67 (95%CI 5.24 – 2.11) (Figure 2). The quality of available evidence is VERY LOW.

2) time to recover TOF>0.9

In the evaluation of the recovery time (min) to reach a TOF ratio >0.9, 20 studies were included, with 855 patients in the SUGAMMADEX group and 812 in the NEOSTIGMINE group.

SUGAMMADEX significantly reduced recovery time from NMB compared to NEOSTIGMINE. A mean risk difference (RD) was found of -12.57 (95%CI 15.12– -10.03) (Figure 3). The quality of available evidence is VERY LOW.

3) Time of permanence in recovery room

In assessing the length of stay in the post-anesthesia care unit (PACU, in min), 6 studies were included, with 364 patients in the SUGAMMADEX group and 370 in the NEOSTIGMINE group.

With SUGAMMADEX, the time spent in the PACU was shorter compared to NEOSTIGMINE. The time reduction was significant, with a mean RD of -9.91 (95%CI -15.66– -4.16) (Figure 4). The quality of available evidence is VERY LOW.

4) Bradycardia

In the evaluation of bradycardia with the use of block-reversing medication, 9 studies were included, with 621 patients in the SUGAMMADEX group and 563 in the NEOSTIGMINE group.

With SUGAMMADEX, bradycardia occurred less frequently when compared with NEOSTIGMINE, with an absolute reduction in the RD of -0.09 (95%CI -0.14– -0.04) (Figure 5). The quality of available evidence is LOW.

5) Hypertension

In the evaluation of arterial hypertension with the use of block-reversing medication, 3 studies were included, with 174 patients in the SUGAMMADEX group and 174 in the NEOSTIGMINE group.

With SUGAMMADEX, hypertension was more frequent when compared with NEOSTIGMINE, with a significant RD of 0.06 (95%CI 0.02–0.11) (Figure 6). The quality of available evidence is VERY LOW.

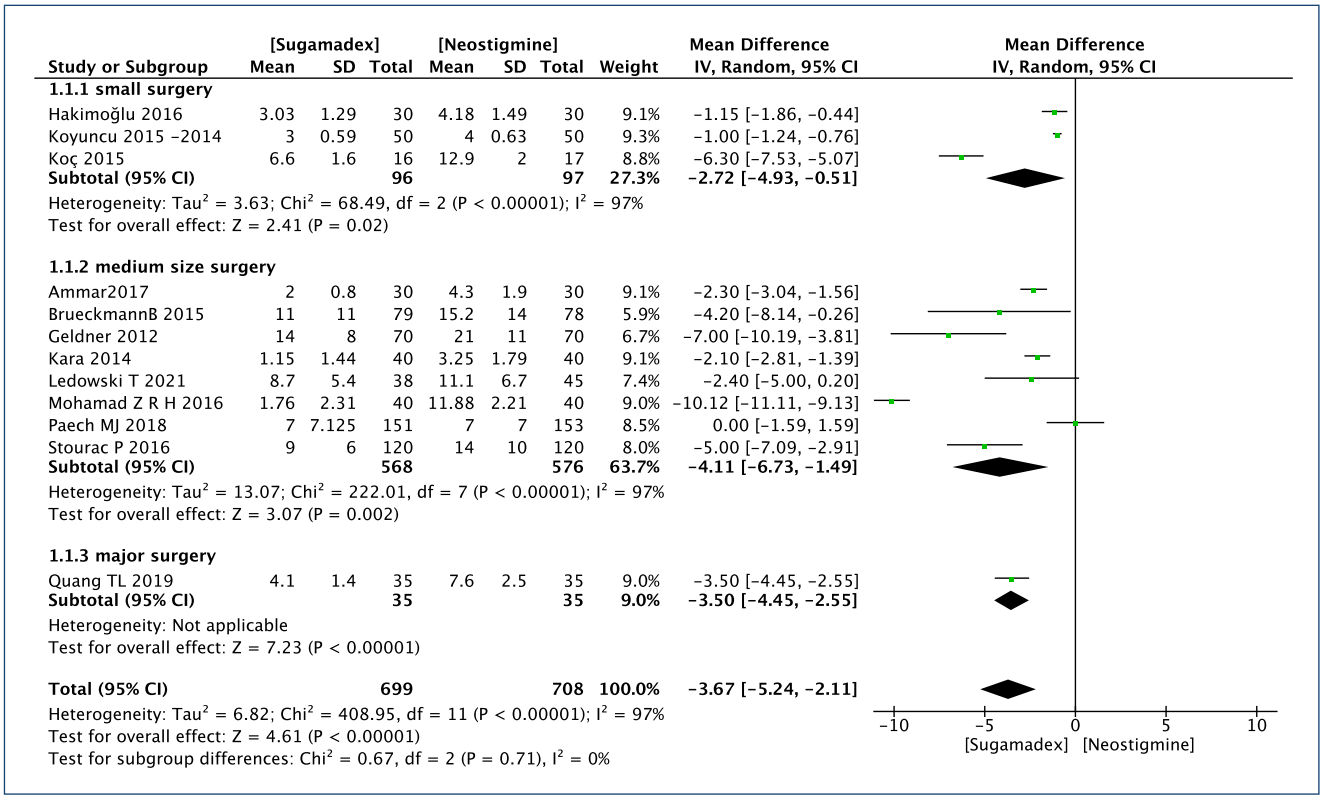

Figure 2. Forest plot comparing sugammadex versus neostigmine in extubation time.

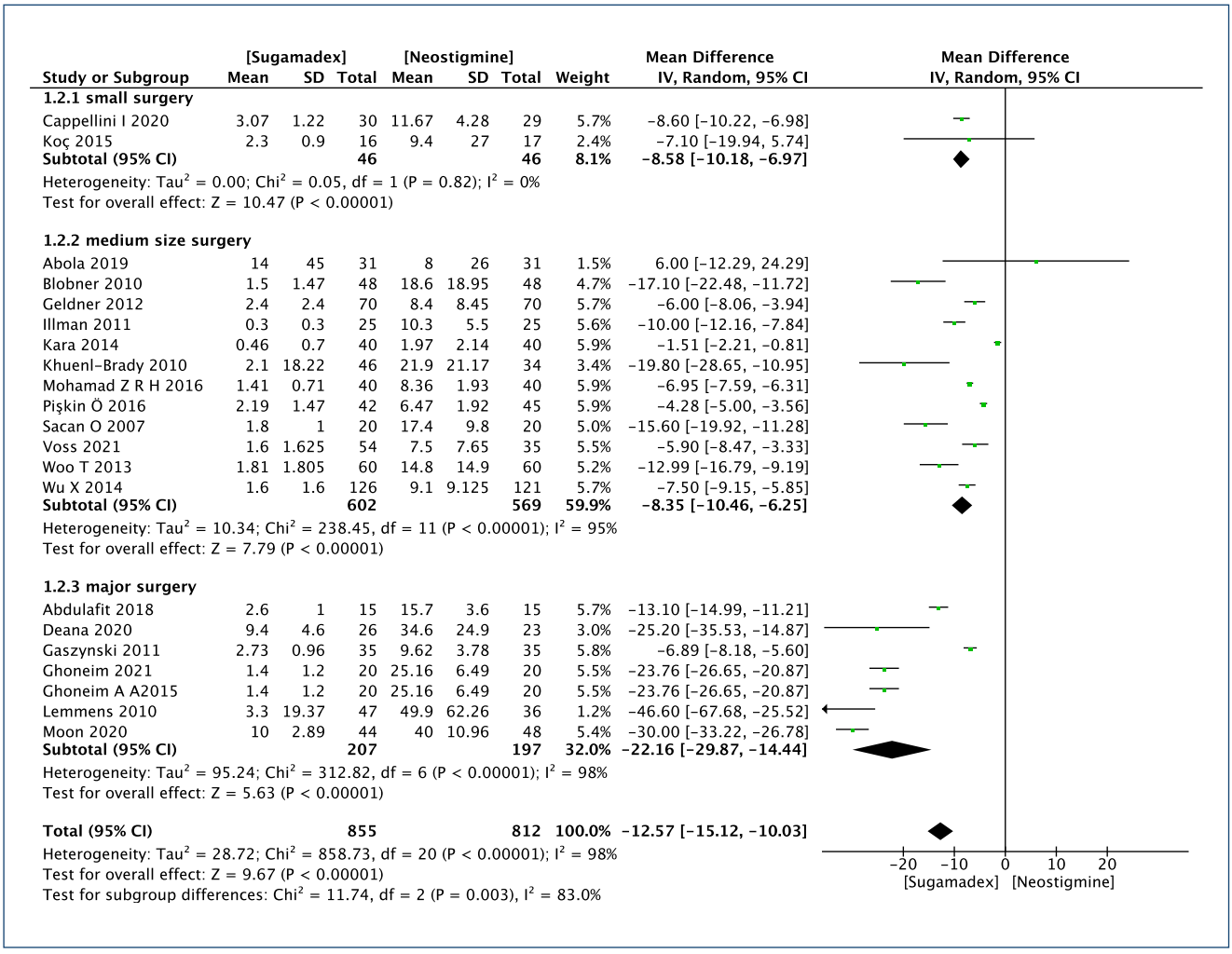

Figure 3. Forest plot comparing sugammadex versus neostigmine in neuromuscular block recovery time.

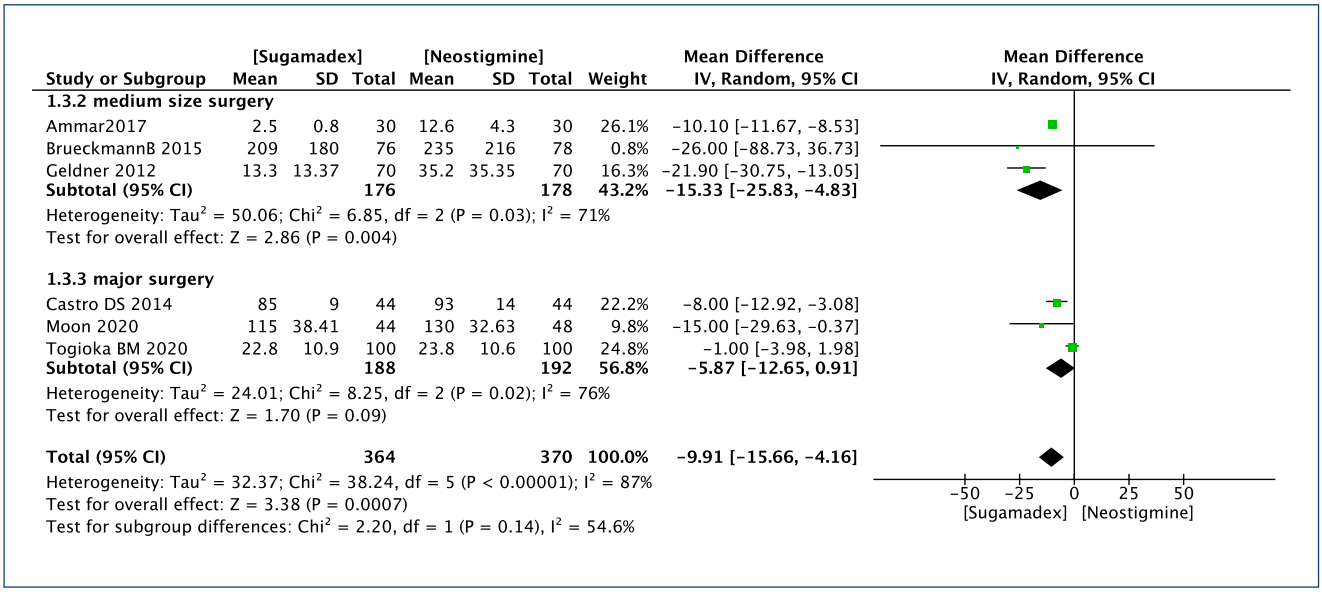

Figure 4. Forest plot comparing sugammadex versus neostigmine in time in the post-anesthesia care unit.

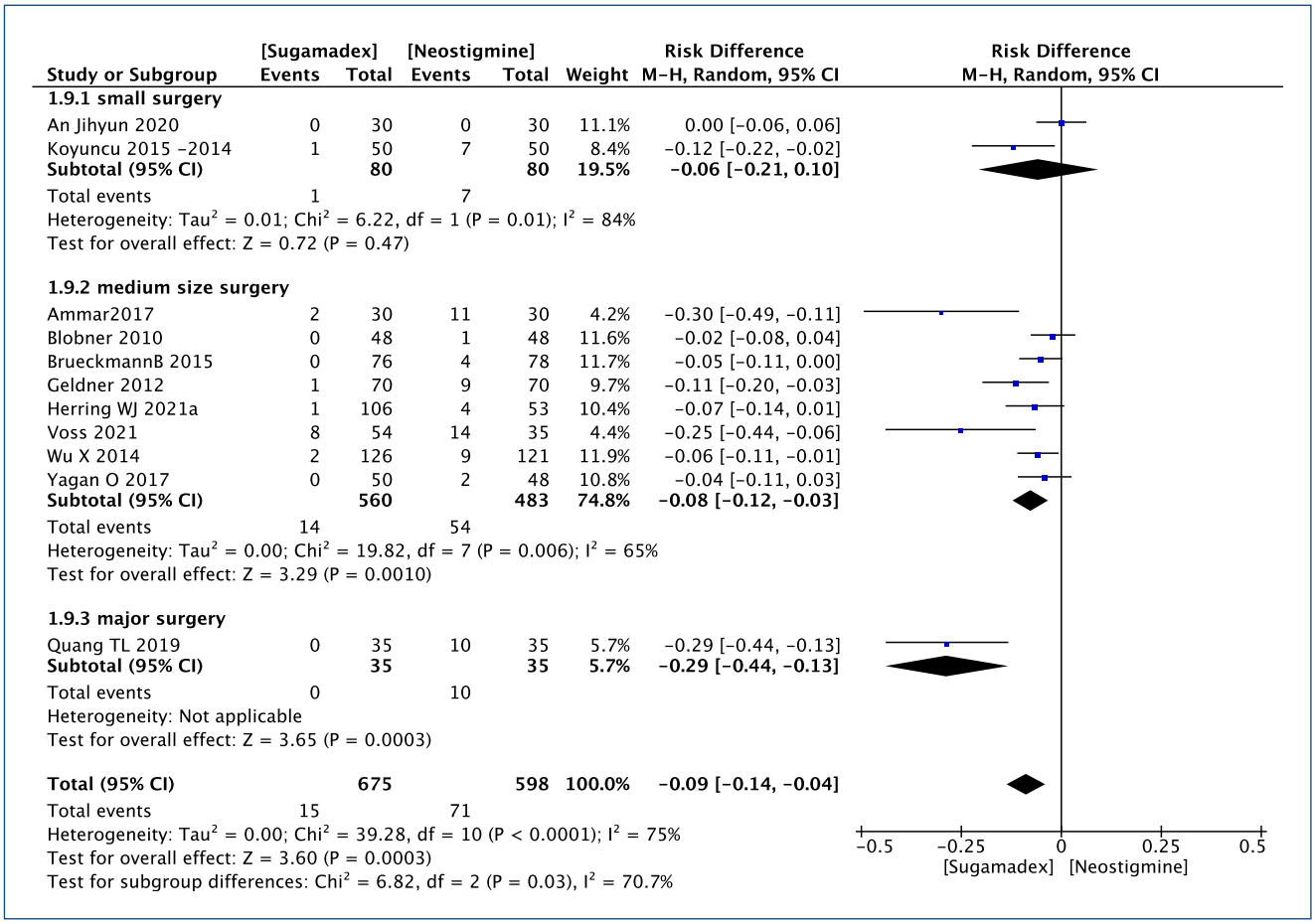

Figure 5. Forest plot comparing sugammadex versus neostigmine in evidence of bradycardia.

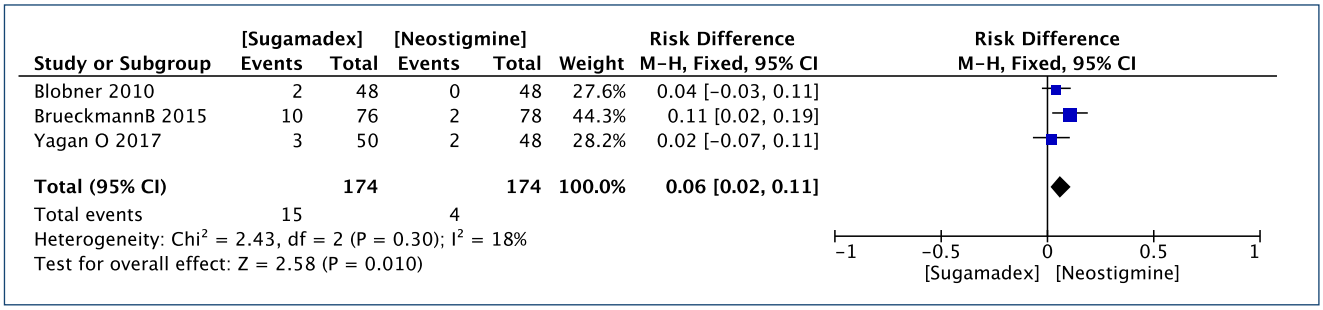

Figure 6. Forest plot comparing sugammadex versus neostigmine in evidence of hypertension.

6) Hypotension

In the evaluation of arterial hypotension with the use of block-reversing medication, 2 studies were included, with 126 patients in the SUGAMMADEX group and 128 in the NEOSTIGMINE group.

For the hypotension outcome, SUGAMMADEX showed no difference compared to NEOSTIGMINE, with an RD of −0.00 (95%CI -0.04–0.03) (Figure 7). The quality of available evidence is MODERATE.

7) Hypoxemia

In the evaluation of hypoxemia with the use of block-reversing medication, 5 studies were included, with 388 patients in the SUGAMMADEX group and 395 in the NEOSTIGMINE group.

For the hypoxemia outcome, there was no statistically significant difference between SUGAMMADEX and NEOSTIGMINE (RD=0.04; 95%CI -0.03–0.12) (Figure 8). The quality of available evidence is VERY LOW.

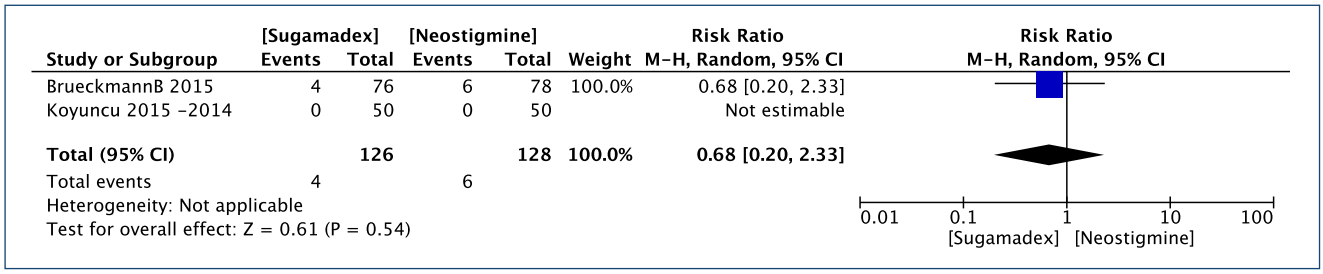

Figure 7. Forest plot comparing sugammadex versus neostigmine in evidence of hypotension.

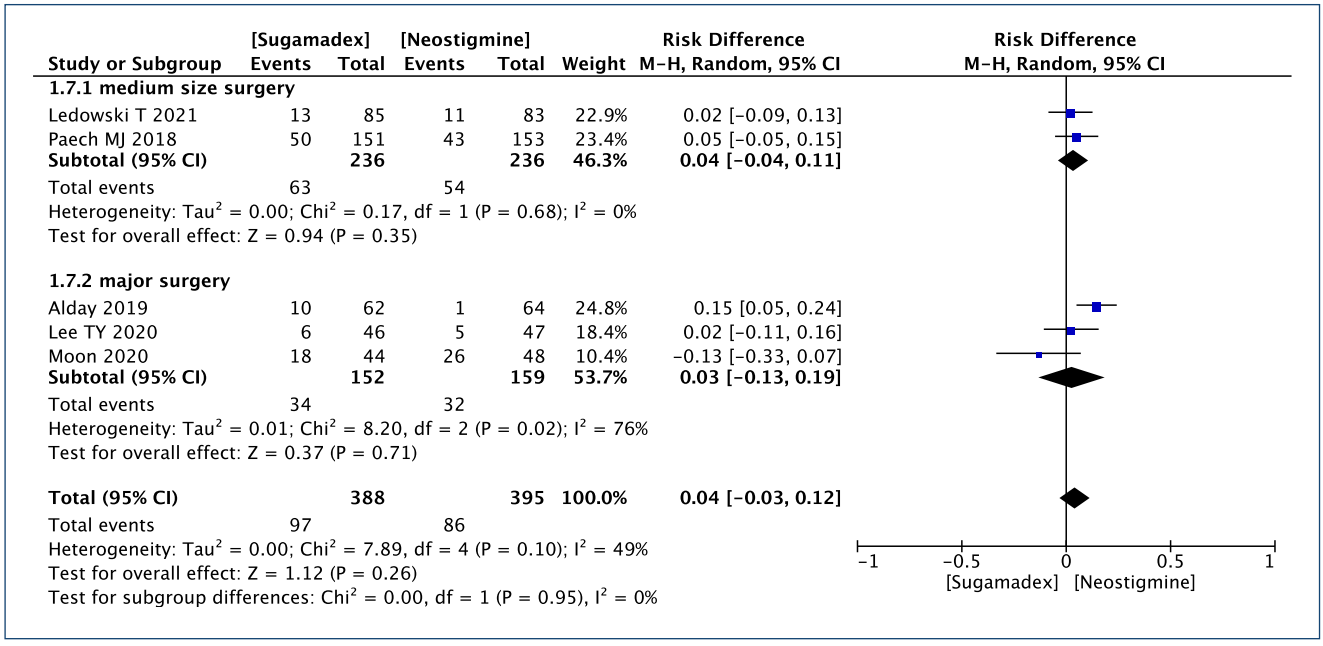

Figure 8. Forest plot comparing sugammadex versus neostigmine in evidence of hypoxemia.

8) Nausea

In the assessment of nausea with the use of block-reversing medication, 14 studies were included, with 819 patients in the SUGAMMADEX group and 800 in the NEOSTIGMINE group.

> No difference was found between the groups that used SUGAMMADEX and NEOSTIGMINE in the incidence of nausea (RD= -0.02; 95%CI -0.05–0.01) (Figure 9). The quality of available evidence is VERY LOW.

9) Vomiting

In the evaluation of vomiting with the use of block-reversing medication, 12 studies were included, with 720 patients in the SUGAMMADEX group and 620 in the NEOSTIGMINE group.

> For postoperative vomiting, there was no statistically significant difference between the SUGAMMADEX and NEOSTIGMINE groups (RD= -0.01; 95%CI -0.05–0.03) (Figure 10). The quality of available evidence is VERY LOW.

Quality of evidence (Appendix 3)

We used the principles of the GRADE approach to prepare an overall assessment of the quality of evidence. For hypotension and bradycardia outcomes, the quality of evidence was moderate. In the outcomes such as time to extubation, recovery time for TOF>0.9, time of permanence in the recovery room, nausea, vomiting, and hypoxemia, the quality of evidence was very low, regardless of the size of surgery or disease severity.

The complete GRADE assessment is available in Appendix 3.

Summary of the evidence

In the evaluation of extubation time in surgeries with NMB, sugammadex was shown to be superior, with a small difference in the analysis of the size of the surgery. The quality of available evidence is very low.

In reversing the block to TOF>0.9, there is benefit from the use of sugammadex, with the best evidence for medium

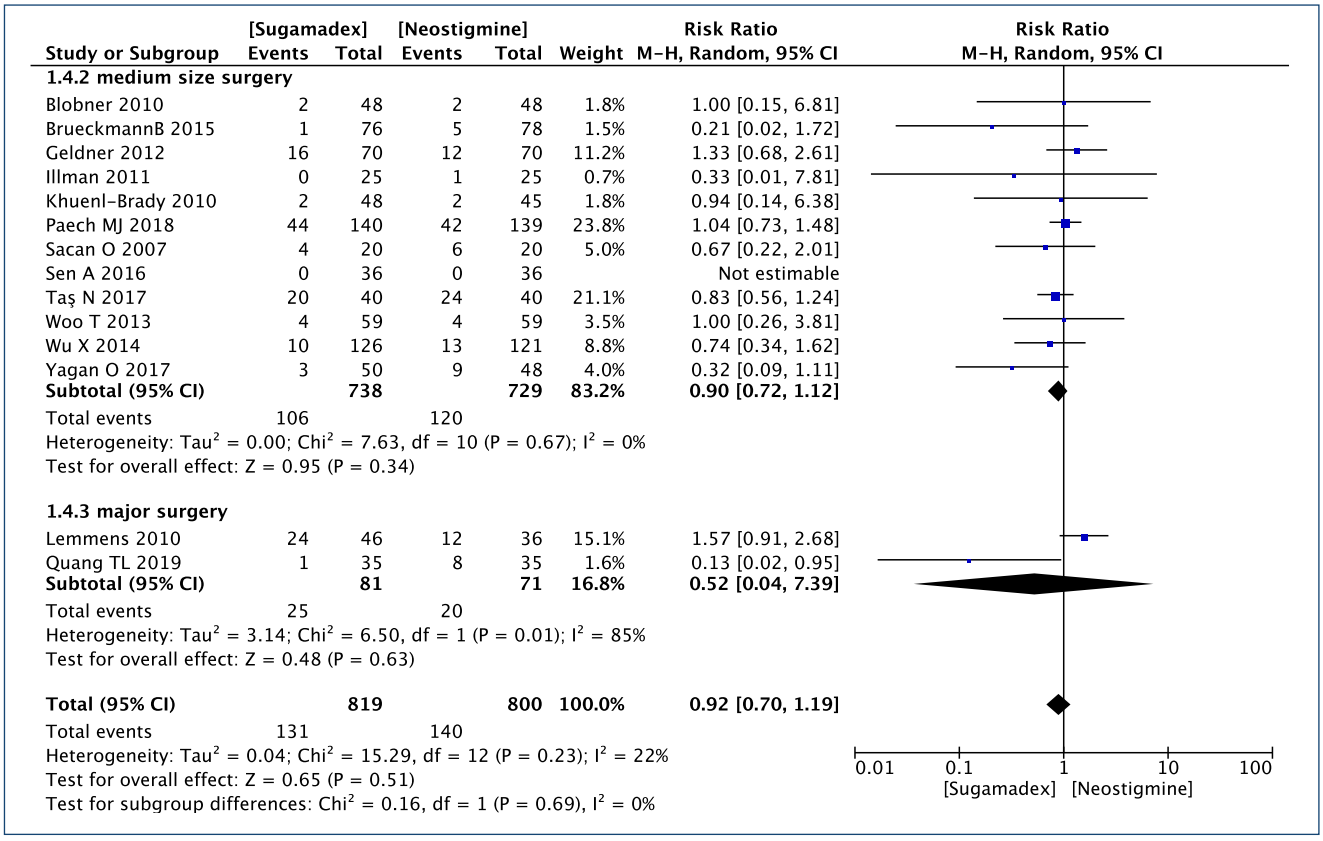

Figure 9. Forest plot comparing sugammadex versus neostigmine in evidence of nausea.

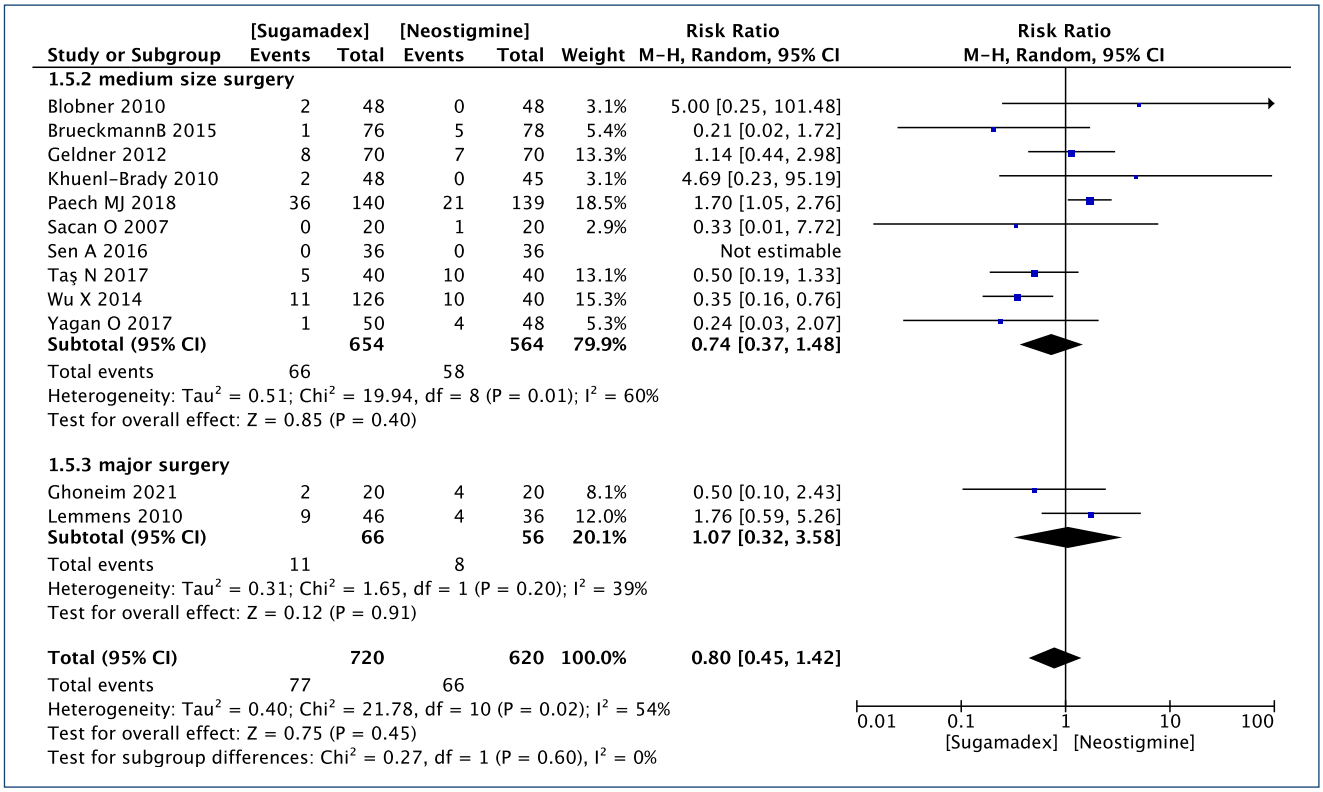

Figure 10. Forest plot comparing sugammadex versus neostigmine in the outcome vomiting.

and large anesthetic surgeries in relation to small surgeries. The quality of available evidence is very low.

For blood pressure indices, the incidence of hypertension was more frequent and significant in the use of sugammadex when compared with neostigmine. The quality of available evidence is very low.

The incidence of hypotension was without significance. The quality of available evidence is moderate.

The incidence of bradycardia was less frequent using sugammadex, with a significant reduction; the RD is -29% in major surgeries and quality of evidence is very low, -6% in medium-sized surgeries, and no difference in small-sized surgeries. The quality of available evidence is low.

For other evaluated events such as nausea, vomiting, and hypoxemia, there is no evidence of an RD in the comparative use of the drugs. The quality of available evidence is very low.

With the exception of the hypertension and hypotension outcomes, in the other evaluations, we showed high heterogeneity, so care should be taken in the interpretation of the results obtained.

DISCUSSION

Numerous studies have compared sugammadex versus neostigmine in the reversal of rocuronium-induced NMB. In the observational cohort study by Kheterpal[60], 45,712 patients were included for this purpose. The outcomes evaluated were pulmonary complications (primary composite outcome), pneumonia, and respiratory failure. The reported results were as follows: for pulmonary complications (primary composite outcome), 1.3% RD reduction (3.5 sugammadex vs. 4.8% neostigmine), with an NNT=77; for pneumonia, there was RD reduction of 0.9% (1.3 vs. 2.2%), with NNT=111; and for respiratory failure, 0.9% RD reduction (0.8 vs. 1.7%), with an NNT=111.

In this systematic review and meta-analysis of 36 RCTs, comparing the efficacy and safety of sugammadex and neostigmine, it was found that sugammadex led to shorter extubation time, shorter recovery time to reach TOF>0.9, and fewer cases of bradycardia. On the other hand, more cases of hypertension were reported in patients in the sugammadex group.

The extubation time outcome with sugammadex was significantly shorter compared to neostigmine, although this difference is only a few minutes (3.67 min, 95%CI -5.24– -2.11). In another meta-analysis, Carron et al.[61] also found a shorter extubation time in the sugammadex group (RD=0.18, 95%CI 0.14–0.22).

When the outcome recovery time to reach TOF>0.9 was evaluated, the meta-analysis composed of 20 studies showed a large and significant difference in NMB reversal time, favoring sugammadex over neostigmine 0.05 mg/kg (-12.57, 95%CI -15.12– -10.03). In the review by Hristovska et al.[62], this time interval was approximately 6.6 times shorter with sugammadex (MD -10.22, 95%CI -11.96– -8.48). Carron et al.[61] evaluating vecuronium-induced NMB reversal confirmed that sugammadex is faster than neostigmine in reversing rocuronium-induced blockade (MD -1.82; 95%CI -2.18– -1.46). In the evaluation of subgroups of these 20 RCTs according to the size of the surgeries, the major surgeries (e.g., cardiac surgery, transplantation, and bariatric surgery) presented a significant and favorable reduction with sugammadex, at the same dosages mentioned above. In medium-sized surgeries, the variation was also significant in favor of the sugammadex group.

Considering the adverse events evaluated, the differences were small. With the use of sugammadex, there was a lower incidence of bradycardia (8%, NNT=12) and a higher incidence of hypertension (6%, NNT=17). Hristovska et al.[62] showed no differences in their review.

For hypotension, nausea, and vomiting outcomes, there is no evidence of differences.

Regarding the high heterogeneity observed in the meta-analysis, we evaluated that although the inclusion criteria were well established and met, the disparities between the selected studies are evident, which may partly explain the high heterogeneity observed in the result. In addition, we cite the difficulty regarding the clinical selection of patients with very different pathologies and wide variation in disease severity. Comparing our meta-analysis with that performed by Cochrane[62], our numbers differ because those authors assessed relative risk and we used RD and MD.

CONCLUSION

The results suggest that sugammadex is as effective in reversing vecuronium or pancuronium-induced NMB as neostigmine, although the time difference in minutes to extubation is very small and the certainty of evidence analyzed using GRADE is low.

In the analysis of time to extubation, time to recover TOF>0.9, and bradycardia, there was statistical significance in favor of sugammadex. The hypertension outcome was unfavorable to sugammadex. However, high heterogeneity was found in the majority of outcomes.

Sugammadex, due to its faster reversal and similar adverse events, appears to have a more favorable safety profile, although the cost is much higher.

We understand that future studies are needed with larger samples and a low risk of bias to confirm the findings reported above.

AUTHORS' CONTRIBUTIONS

AA: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **AU:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **GT:** Conceptualization, Writing – review & editing. **HK:** Conceptualization, Writing – original draft, Writing – review & editing. **IAZS:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **LST:** Conceptualization. **MMN:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **MA:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **OST:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **PRNS:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **PO:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **WMB:** Conceptualization, Data curation, Formal Analysis, Writing – original draft.

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APPENDIX 1

Characteristics of the studies

Abdulafit 2018[10]

Adult patients with liver resection with or without cirrhosis, being randomized (60); sugammadex 2 mg/kg (30) × neostigmine 50 μg/kg + atropine 20 μg/kg (30), being evaluated the recovery time (TOF 0.9), length of stay in recovery, and postoperative recurarization, with follow-up time being the time to reach TOF.

Abola 2019[11]

Randomized clinical trial in adult patients for surgery requiring neuromuscular block, endotracheal intubation and extubation at recovery (n=62), sugammadex 2–4 mg/kg (n=31) × neostigmine 70 μg/kg + glycopyrrolate 10 μg/kg were evaluated (n=31). The outcomes evaluated were block reversal by spirometry, handshake, sit down, and sedation level (RASS); follow-up time was recovery time 30, 60, and 120 min.

Alday 2019[12]

Adults who underwent major abdominal surgery (n=130) were randomized comparing sugammadex 4 mg/kg (n=65) and neostigmine 40 μg/kg + atropine 10 μg/kg (n=65), being evaluated as an outcome reversal of the spirometry block, hypoxemia, nausea, and vomiting. Follow-up time was 60 min.

Ammar 2017[13]

Pediatric patients who underwent surgery on the lower abdomen (60), randomized comparing: sugammadex 4 mg/kg (30) versus neostigmine 35 μg/kg + atropine 2 μg/kg (30). Outcomes evaluated: time to recovery (TOF 0.9), extubation time, length of stay in recovery, and adverse events. Follow-up time: time to outcome.

An Jihyun 2020[14]

Children with entropion surgery randomized (n=60), comparing sugammadex 2 mg/kg (n=30) and pyridostigmine 20 μg/kg + glycopyrrolate 1 μg/kg (n=30). Outcomes evaluated: time to recovery (TOF 0.9); extubation time; adverse events. Follow-up done was time for the outcome.

Blobner 2010[15]

Adult patients randomized (n=98) to elective surgical procedure under general anesthesia with ASA I to III classification and any body weight. Divided into sugammadex group with 49 patients and neostigmine with 49 patients. In the reversal of neuromuscular blockade, in the sugammadex group, medication at a dose of 2.0 mg kg IV, and in the neostigmine group, medication at a dose of 50 and 10 mg/kg IV glycopyrrolate, in an alveolar concentration of sevoflurane less than 1.5 in the administration of the reverser. Outcomes evaluated were neuromuscular monitoring until recovery of TOF at 0.9 (T2), heart rate (HR) and blood pressure (BP) were recorded before and 2, 5, 10, and 30 min after medication. Oxygen saturation rate, patients' levels of consciousness, and muscle weakness were also monitored.

Brueckmann B 2015[16]

Randomized clinical trial that studied 154 adult patients for elective laparoscopic or open abdominal surgery, under general anesthesia with rocuronium-induced neuromuscular blockade (NMB). Included ASA class I to III patients. In the sugammadex group, the reversal of deep NMB was performed with a dose of 4 mg/kg, and in moderate, it was with a dose of 2 mg/kg (n=76). In the neostigmine/glycopyrrolate group in NMB reversal, a maximum dose of 5 mg/kg was used (n=78). Primary end point was the presence of residual neuromuscular block, defined by TOF<0.9 on arrival at the PACU. Secondary outcome was the time interval from initiation of medication to being ready to be discharged from the operating room with clinical observance of regular breathing pattern, oxygen saturation, and hemodynamic stability.

Cappellini I, 2020[17]

In this RCT, 59 patients aged between 18 and 80 years with ASA I and II undergoing laryngeal microsurgery with deep NMB with rocuronium were included. Patients with a history of liver disease or renal disease (glomerular filtration <50 ml/min), alcoholism, allergy or hypersensitivity to CNS medications or medications, neurological disease, diaphragmatic paralysis, pregnancy, breastfeeding, or arrhythmic disease were excluded. SUG group with 30 patients received 2 mg/kg of sugammadex IV in identical syringes, and in the NEO group, 29 patients received 50 mg/kg neostigmine and 15 mg/kg atropine IV in identical syringes. Primary outcome was to assess residual neuromuscular blockade at 30 min after administration of reversal drugs.

Castro DS Jr[18]

A total of 88 adult obese patients were randomized to elective laparoscopic video gastroplasty surgery under general anesthesia with neuromuscular blockade (NMB). Patients with chronic pain and those already enrolled in another study of anterior laparoscopy surgery were excluded due to a lack of consent. The reversal of NMB in the sugammadex group with 44 patients was with 2 mg/kg correcting the body weight (CBW) of the medication. The NMB reversal in the neostigmine group with 44 patients was used 0.05 mg/kg (CBW) + atropine 0.02 mg/kg (CBW) of the medication. Main outcome evaluated was extubation in TOF-T2 (>0.9). Pain was assessed using the VAS scale on arrival at RPA, at 30 and 60 min after arrival. Assessed by the Aldrete Scale, a score greater than 9 defined high RPA and nausea and vomiting postoperative omits (PONV).

Dean 2020[19]

This is an unblinded randomized clinical trial with patients undergoing liver transplantation with the primary objective of evaluating the recovery time of neuromuscular transmission obtained with sugammadex versus neostigmine after rocuronium-induced neuromuscular blockade. NMB reversal in the sugammadex group was used 2 mg/kg based on actual body mass index (BMI) with 26 patients and in the neostigmine group with 50 mcg/kg (BMI) adjusted + 10 mcg/kg atropine with 23 patients. The primary end point assessed was the time interval from agent administration to reversal on three consecutive measurements with TOFR≥0.9. Secondary outcome was to analyze the main possible correlations between factors that may have influenced the recovery time of sugammadex and neostigmine.

Gaszynski 2011[20]

Randomized clinical trial that studied 70 morbidly obese adult patients (BMI=0.40 kg/m²) for elective surgical procedure for bariatric surgery. Exclusion criteria were lack of consent, muscle diseases, and severe cardiovascular diseases. NMB reversal in the sugammadex group, 2 mg/kg (CBW) of the medication was used with 35 patients and in the neostigmine group with 35 patients, 0.05 mg/kg CBW + atropine 0.02 mg/kg (CBW) was used. Outcome assessed was the mean time to reach 90% in TOF T2 (>0.9).

Geldner 2012[21]

Randomized, multicenter, active controlled clinical trial, blinded assessor, protocol assessment, 140 patients undergoing scheduled laparoscopic cholecystectomy or appendectomy under general anesthesia, >18 years, ASA I–III, sugammadex 4 mg/kg (n=70) and neostigmine 50 μg/kg in combination with atropine 10 μg/kg (n=70), with the primary efficacy end point being the time from initiation of sugammadex or neostigmine administration to recovery of the TOF to 0.9. Secondary outcome parameters included safety and length of stay in the operating room and postanesthesia care unit following study drug administration. Safety was assessed by adverse events, vital signs, and physical examination.

Ghoneim 2021[22]

Pediatric patients undergoing elective craniotomy scheduled for posterior fossa tumor excision, ASA I–III, 7–18 years (n=40), sugammadex 4 mg/kg (n=20), and neostigmine 0.04 mg/kg combined with atropine 0.02 mg/kg (n=20). The study's primary end point was the time from administration of sugammadex or neostigmine to recovery of the TOF ratio to 90% after rocuronium-induced neuromuscular blockade.

Intraoperative heart rate and blood pressure during administration of reversal agents were considered secondary outcomes, as well as any incidence of adverse events in the first 24 h after surgery.

Hakimoğlu 2016[23]

Randomized clinical trial, analysis by intention to treat arthroscopic surgery under general anesthesia.
Patients aged 18–65 years (n=60), sugammadex (4.0 mg/kg) (n=30) versus neostigmine (50 mg/kg) plus atropine (15 mg/kg) (n=30). The primary efficacy end point for extubation was the time from administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.9. Operating time (time from skin incision to end of surgery) and adverse events (choking, nausea, vomiting, breath holding, laryngospasm, and tremors).
Hemodynamic parameters (heart rate, mean arterial pressure, peripheral arterial oxygen saturation) were measured before induction and 30 s, 2 min, 10 min, and 30 min after extubation; IOPs were measured before induction and 30 s, 2 min, and 10 min after extubation. Those with a baseline IOP of >30 mmHg were excluded. The Tono-Pen XL applanation tonometer (Medtronic Solan, Jacksonville, FL, USA) was used to measure IOP.

illman 2011[24]

Randomized, double-blind clinical trial, with sample and power calculation, performed in elective surgery with general anesthesia, adult patients (18–70 years), ASA I–IV, BMI <32.5 (n=50), sugammadex 2.0 mg/kg (n=25) versus neostigmine 50 μg/kg + glycopyrrolate 10 μg/kg (n=25).
Primary end point was the time interval between the loss of visual fading to the return of a TOF ratio of 0.90. Secondary end points were times to return of TOF ratio to 0.70, 0.80, and 0.90 after reversal, TOF ratio at loss of visual fading, and time of tracheal extubation. The times from loss of visual fade to return of a TOF ratio of 0.70 and 0.80 and the time from tracheal extubation to return of a TOF ratio of 0.9, follow-up until hospital discharge were also recorded.

Kara 2014[25]

Randomized, double-blind clinical trial of elective outpatient surgery, such as lower abdominal or urogenital surgery in ASA I children (n=80), comparing sugammadex 2 mg/kg (n=40) and atropine 0.01 mg/kg and neostigmine 0.03 mg/kg.
Reversal time was evaluated o since last neuromuscular blocker (NMB) administration (min), extubation time since last NMB administration (min), TOF ratio before reversal, TOF ratio during extubation.

Khuenl-Brady 201026

Randomized clinical trial with 93 patients aged ≥18 years, ASA 1–3, comparing sugammadex (2 mg/kg) with neostigmine (50 μg/kg) + glycopyrrolate (10 μg/kg). The following were evaluated: time to recovery to TOF index=0.9, time to recovery to TOF index=0.7 and 0.8, and signs of recovery (level of consciousness, head elevation test, generalized muscle weakness). And the follow-up was for 7 days of adverse effects.

Koyuncu 2015 -2014[27]

In this study, 100 adult patients, ASA 1/2 with extremity surgery compare sugammadex (2 mg/kg) with neostigmine (70 μg/kg) + atropine (0.4 mg/kg). The outcomes evaluated were PONV scale, clinical recovery, time to extubation, eye opening, head raising, flatus elimination, oral intake and ambulation, side effects, and amount of anti-emetics used in 24 h.

Ledowski T, 2021[28]

A total of 180 adult patients were evaluated, comparing sugammadex (2 mg/kg) to neostigmine (0.05 mg/kg) + atropine (0.015 mg/kg), with the following outcomes: pulmonary outcome score, clinical recovery (time to extubation), acute postoperative complications (desaturation, aspiration, signs of muscle weakness, and PONV score), length of hospital stay, and 30-day mortality.

Lee TY 2020[29]

A total of 93 patients aged ≥18 years, undergoing video-assisted lobectomy, ASA 1–3, were randomized evaluating sugammadex (2 mg/kg) and neostigmine (0.05 mg/kg) + atropine (0.02 mg/kg). Outcomes evaluated: incidence of postoperative pulmonary complications (presence of prolonged air fistula, pneumonia, atelectasis, desaturation, and reintubation), length of hospital stay, and length of stay in the ICU in 10 days.

Lemmens 2010[6]

Randomized trial with 81 patients ≥18 years, ASA 1–4, sugammadex (4 mg/kg) compared to neostigmine (70 μg/kg) + glycopyrrolate (14 μg/kg), the outcomes being time to recovery up to TOF=0, 9, time to recovery to TOF index=0.7 and 0.8, and signs of recovery (level of consciousness, head lift test, generalized muscle weakness), as well as adverse effects.

Moon 2020[30]

Comparative trial of sugammadex 2 mg/kg (maximum 200 mg) with neostigmine 40 μg/kg (maximum 5 mg) + glycopyrronium 400 μg. The primary end point was cumulative incidence of PONV from awakening to 6 h after surgery. Follow-up: time to completion.

Paech MJ 2018[31]

Randomized, blinded, controlled clinical trial, whose participants were 304 women aged 18–70 years undergoing general anesthesia for laparoscopic gynecological surgery; we compared the characteristics of postoperative recovery with the use of sugammadex and neostigmine/glycopyrrolate in the reversal of neuromuscular blockade. Nausea and vomiting in the first 6 h postoperatively, the intensity of such symptoms as well as the quality of postoperative recovery were evaluated.

Pişkin Ö, 2016[8]

Prospective, randomized study (sealed envelope method), double-blind and controlled; included 87 patients aged 18–60 years who underwent general anesthesia for abdominal surgery, upper extremity orthopedic interventions, gynecological, plastic, urological, otolaryngological, and spinal surgery lasting approximately 60 min. By comparing the effect of sugammadex against neostigmine, the study aimed to assess whether faster awakening from general anesthesia would influence cognitive functions in the immediate postoperative period. The information contained in the study clarifies the time required to reach the TOF 90% and time to recovery.

Quang TL, 2019[5]

Randomized controlled study composed of 70 patients between 18 and 70 years of age, ASA I–III, donor candidates for nephrectomy and under general anesthesia. We compared the action of sugammadex in relation to the combination of neostigmine + atropine sulfate on neuromuscular blockade along with the side effects presented. The time required for neuromuscular block reversal was analyzed according to TOF >0.9 and postoperative side effects such as cardiovascular changes, headache, nausea, bronchial secretion, and xerostomia.

Sacan O 2007[32]

Randomized trial, 60 adult patients, ASA I–III, elective surgical procedures requiring intubation using neostigmine (70 μg/kg) with glycopyrrolate (14 μg/kg) or edrophonium (1 mg/kg) with atropine (10 μg/kg) versus sugammadex (4 mg/kg). Outcomes assessed: TOF time 0.7, 0.8, and 0.9, heart rate, medial blood pressure, change in MAP (%) in 2 min, dry mouth, muscle weakness, and head elevation.

Taş N, 2017[33]

Randomized, double-blind clinical trial that studied 80 patients aged 18–65 years who underwent laparoscopic cholecystectomy under anesthesia. General care (anesthesiologist was blinded) and neuromuscular blockade with rocuronium 0.6 mg/kg. Patients with wing greater than or equal to III, age below or above 65 years, BMI >30 kg/m^2, and hypersensitivity to any one were excluded from study, such as drugs, history of PONV, high risk for PONV (Apfel score greater than II), patients who were pregnant or menstruating, and those who had taken antiemetic medication in the last 24 h. In the sugammadex group, NMB reversal was performed at a dose of 2 mg/kg. In the neostigmine group, NMB reversal was performed with a dose of 0.04 mg/kg and 0.015 mg of atropine. All patients were extubated with a TOF ratio >90%. The primary end point was the assessment of nausea and vomiting (PONV) from 0 to 24 h postoperatively.

Togioka BM, 2020[34]

This study is an RCT, randomized, evaluator blinded, envelope allocation, anesthetist blinded, IT analysis. We studied 200 patients with eligibility criteria of age over 70 years, scheduled surgery lasting 3 h or more and without contraindications for NMB.

Exclusion criteria included significant kidney disease (stage 4 kidney disease or greater), significant liver disease (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] greater than twice the upper limit of institutional normal), allergies to study drugs, and refusal of consent. Written informed consent was obtained from all enrolled subjects.
The primary outcome measure was to assess postoperative complications from lung surgery. Secondary end points included residual paralysis (train-of-four ratio=0.9) and recovery from Phase 1 (time to pain control stable respiratory, hemodynamic, and neurological status). Additional end points were length of hospital stay, proportion of patients with hospital readmission within 30 days; and proportion of patients diagnosed with a respiratory disease complication, as defined by the National Surgical Quality Improvement Program (postoperative pneumonia, unplanned intubation, ventilator dependence >48 h).
Residual neuromuscular blockade is associated with airway obstruction, hypoxemia, atelectasis, and pneumonia. Furthermore, even low levels of neuromuscular blockade (sequence rate of four [TOF] <0.9 or 0.95) in healthy volunteers not exposed to anesthesia or surgery were associated with pharyngeal-laryngeal dysfunction and depressed hypoxic ventilatory drive. Reducing residual neuromuscular blockade may decrease postoperative pulmonary complications.

Woo T 2015[37]

RCT, randomized, evaluator blinded, analysis by IT that studied 118 Korean patients, over 18 years of age and wing 1,2,3. All patients were of Korean descent, born in Korea, never having left Korea and with a Korean home address. Exclusion criteria were any anatomic malformation that could cause difficult intubation; any patient transferred to the intensive care unit after surgery; neuromuscular disorders that can affect NMB; significant renal or hepatic dysfunction; requirement for a pneumatic tourniquet during surgery; (family) history of malignant hyperthermia; allergy to opioids/opiates, cyclodextrins including sugammadex, muscle relaxants and their excipients, or other drugs used during general anesthesia; administration of toremifene and/or fusidic acid within 24 h of study drug administration (or plan to administer these drugs within 24 h of study drug administration); any condition against the indication of neostigmine and/or glycopyrrolate; pregnant women; participation in a previous study of sugammadex; participation in another clinical drug study within 30 days, including after signing consent for the current study; or a member of or related to the investigation team or the sponsor's team.
Undergoing nose, ear, and larynx surgery, gynecological and digestive system surgeries; under general anesthesia and use of NMB rocuronium at a dose of 0.6 mg/kg for OTI and 0.1–0.2 mg/kg for maintenance. The anesthesiologist was not blinded, compromising allocation, randomization, and double blinding. In the sugammadex group, NMB reversal was performed with a dosage of 2 mg/kg IV after the end of the surgery. In the neostigmine group, NMB reversal was performed at a dose of 50 mcg/kg (total dose should not exceed 5 mg) combined with glycopyrrolate at a dose of 10 mg/kg IV after the end of surgery.
The primary end point is the measure of time of NMB reversal from initiation of drug administration to recovery. (T4/T1=0.9.), evaluating efficacy in Korean patients. Secondary end points included time to recovery from the TOF ratio to 0.7 and 0.8. The timing of T2 reappearance after the last dose of rocuronium was also evaluated. Effect adverse events such as nausea and vomiting, as well as others were evaluated. Previous work with Caucasian populations was compared with the results of this work.

Wu X. 2014[35]

This work is an RCT, multicenter, blinded evaluator, analysis by IT. A total of 308 patients were studied, 247 Chinese and 61 Caucasian aged between 18 and 64 years and ASA I/III. All Chinese were from China, never emigrated out of China, and had domestic addresses in China. The same criteria were extended to Caucasians in relation to Europe. Patients with anatomic malformations that could lead to difficult tracheal intubation, neuromuscular disorders affecting NMB, significant renal/hepatic dysfunction (as determined by the investigator), (family) history of malignant hyperthermia, and allergy to anesthetic medications were excluded from the study. In general, contraindication to study drugs, or a clinically significant condition that may interfere with the trial (as determined by the investigator).
The groups were randomized using a central randomization system. A computer-generated randomization schedule with block treatment codes, using a validated SAS-based application. The schedule associated each treatment code with a PAC number, and patients were randomized in a 1:1 ratio to receive sugammadex 2 mg/kg or neostigmine 50 μg/kg with atropine 10–20 μg/kg.
After induction of anesthesia, but before administration of rocuronium, neuromuscular monitoring was performed using continuous acceleromyography on the adductor thumb muscle using the TOF-Watch® SX.

The primary end point was the time from initiation of sugammadex or neostigmine/atropine administration to recovery from the TOF index to 0.9. The secondary end point included time to recovery from the TOF ratio to 0.7 and 0.8. Studies of adverse effects such as nausea, vomiting, bradycardia, hypotension, and cardiac complications were performed.

Yagan O 2017[9]

This prospective, randomized, controlled, double-blind study was performed with 98 patients, ASA I and II, aged between 18 and 65 years, scheduled for elective surgery with general anesthesia and endotracheal intubation. Envelope allocation compromised randomization. Exclusion criteria were: neurosurgery; laparoscopy; oncological, gynecological and breast surgery; strabismus and middle ear surgery; history of drug and alcohol abuse; body mass index (BMI) >30 kg/m^2; use of analgesics, sedatives or antiemetics in the 24 h before surgery; psychiatric and neurological diseases; allergy or contraindication to study drugs. Patients who underwent surgery longer than 2 h were also excluded.

At the end of the surgery, the administration of the anesthetic agent was suspended and the patient was manually ventilated with 100% oxygen. In accordance with the randomization procedure, reversal of neuromuscular blockade was provided with intravenous administration of neostigmine (0.05 mg/kg) and atropine (0.02 mg/kg) for patients in Group N and sugammadex (2 mg/kg) for patients in Group S, at the reappearance of the second contraction (T2) in the TOF. The patients were extubated after aspiration of secretions from the oropharynx, with a recovery of 90% of the TOF value. Additional IV administration of neostigmine (0.025 mg/kg) and atropine (0.01 mg/kg) in Group N and sugammadex (2 mg/kg) in Group S was planned, if necessary (TOF value below 90% after 5 min).

The primary outcome of our study was that using sugammadex to antagonize the effects of neuromuscular blocking agents would reduce nausea and vomiting compared with neostigmine. Adverse effects such as hypertension, bradycardia, respiratory depression, and others were evaluated.

Ghoneim A.A 2015[36]

A total of 40 pediatric patients were randomly enrolled in this study at Children Cancer Hospital Egypt (CCHE) and those selected with physical status ASA I–III between 7 and 18 years for elective craniotomy and posterior fossa tumor excision. They were randomly allocated to one of two groups (20 patients each): neostigmine and sugammadex group – group in which muscle relaxation was reversed at the end of surgery using neostigmine 0.04 mg/kg combined with atropine 0.02 mg/kg or sugammadex 4 mg/kg only, respectively. The primary study end point was the time from administration of sugammadex or neostigmine to recovery of the TOF ratio to 90% (0.9) after rocuronium-induced neuromuscular blockade.

Mohamad Zaini R.H. 2016[37]

The purpose of this study is to compare recovery time, hemodynamic stability, and complications between two reversal agents, i.e. sugammadex and neostigmine, in antagonizing the effects of rocuronium in the pediatric population. A double-blind, randomized, controlled trial involving 80 children aged 2–12 years for elective surgery under general anesthesia and neuromuscular block rocuronium uromuscular They were randomized into two groups by reversal with neostigmine or sugammadex. Pre- and post-reversion hemodynamic parameters were documented. Patients were reversed according to allocated group – 0.05 mg/kg neostigmine with 0.02 mg/kg atropine or 2 mg/kg sugammadex. A neuromuscular recovery time for TOF ratio of 0.9 has been documented. Patients were extubated at TOF 0.9, any complications observed after extubation were also documented. Results were reported.

Koç 2015[38]

Abstract work where 33 patients aged between 18 and 65 years were evaluated, randomly distributed, ASA I–III, submitted to short-term surgery comparing sugammadex 2 mg/kg (n=16) versus neostigmine 50 g/kg with atropine 20 g/kg (n=17).

Herring WJ 2021[39]

Randomized, active-controlled trial, double-blind safety study, multiple sites, parallel group, conducted at 27 sites in 4 countries from December 2017 to September 2019. Included were men and women aged 18 years or older, more with BMI <40 m²/kg, and ASA 3 or 4 for elective surgeries involving moderate or deep block with rocuronium or vencuronium. Participants were randomized into treatment groups. Moderate neuromuscular blockade and reversal with sugammadex 2 mg/kg; moderate neuromuscular

blockade and reversal with neostigmine (50 µg/kg up to 5 mg maximum dose) plus glycopyrrolate (10 µg/kg up to 1 mg maximum dose). Primary end points included incidences of treatment-emergent sinus bradycardia (TE), sinus tachycardia (TE), and other cardiac arrhythmias (TE).

Voss 2021[40]

Randomized clinical trial, phase IV, with patients aged 2–<17 years, ASA I–III, 288 patients were divided into three groups: (1) moderate block and reversal with sugammadex 2 mg/kg (N=51); (2) moderate block and reversal with neostigmine methyl sulfate 50 µg/kg plus glycopyrrolate 5–15 µg/kg or atropine sulfate 10–30 µg/kg (active control – N=34), or (3) deep block and reversal with sugammadex 4 mg/kg (N=191). The primary end point was TOF recovery time ≥0.9, and clinically relevant bradycardia, hypersensitivity, and anaphylaxis were also assessed.

APPENDIX 2

Risk of bias and quality of evidence

Table 1. Analysis of the risk of bias of the included works.

Author/year	Randomi-zation	Allocation sold	Double blind	Evaluator blinding	Losses	Characteristics prognosis	Outcomes	AIT	Sample calculation	Early INTERRUPTION
Abdulafit 2018										
Abola 2019										
Alday 2019										
Alseed 2017										
Ammar2017										
An Jihyun 2020										
Batistaki 2017										
Blobner 2010										
Brueckmann B 2015										
Cappellini I 2020										
Castro DS, 2014										
Deana 2020										
Gaszynski 2011										
Geldner 2012										
Ghoneim 2021										
Hakimoğlu 2016										
Ilmann 2011										
Kara 2014										
Khuenl-Brady 2010										
Koyuncu 2014										
Ledowski T, 2021										
Lee TY 2020										
Lemmens 2010										
Moon 2020										
Paech 2017										
Piskin 2014										
Quang 2019										
Sacan 2007										
Sen 20										
Stourac 2015										
TAS N 2017										
TOGIOKA BM 2020										
Woo T 2013										
Wu X 2014										
YAGAN O 2017										
Ghoneim A.A 2015										
Mohamad Z R.H. 2016										
Herring WJ 2021										
Koç 2015										
Voss 2021										

AIT: analysis by intention of treatment.

NO BIAS
ABSENCE OF INFORMATION
PRESENCE OF VIES

APPENDIX 3

Author(s):

Question: Sugammadex × neostigmine compared to placebo for anesthesia general

Setting:

Bibliography: Sugammadex versus neostigmine for anestesia geral. Base de Dados de Revisões Sistemáticas da Cochrane [Year], Número [Issue].

Certainty assessment							№ of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sugammadex × neostigmine	placebo	Relative (95%CI)	Absolute (95%CI)		
Extubation time												
12	Randomized trials	Very serious[a,b,c]	Not serious	Serious[c]	Not serious	None	699	708	-	MD **3.67 lower** (5.24 lower to 2.11 lower)	⊕◯◯◯ Very low	
Extubation time – small size												
3	Randomized trials	Very serious[a,b,c]	Not serious	Serious[c]	Not serious	None	96	97	-	MD **2.72 lower** (4.93 lower to 0.51 lower)	⊕◯◯◯ Very low	
Extubation time – midsize												
8	Randomized trials	Very serious[a,b,c]	Not serious	Serious[c]	Not serious	None	568	576	-	MD **4.11 lower** (6.73 lower to 1.49 lower)	⊕◯◯◯ Very low	
Extubation time – large size												
1	Randomized trials	Very serious[a,b,c]	Not serious	Serious[c]	Not serious	None	35	35	-	MD **3.5 lower** (4.45 lower to 2.55 lower)	⊕◯◯◯ Very low	
1.1 Recovery time to reach TOF 90% (0.9)												
20	Randomized trials	Very serious[a,b,c]	Not serious	Serious[c]	Not serious	None	801	777	-	MD **12.98 lower** (15.63 lower to 10.33 lower)	⊕◯◯◯ Very low	
1.1 Recovery time to reach TOF 90% (0.9) – small size												
2	Randomized trials	Very serious[a,b]	Not serious	Serious[c]	Not serious	None	46	46	-	MD **8.58 lower** (10.18 lower to 6.97 lower)	⊕◯◯◯ Very low	
1.1 Recovery time to reach TOF 90% (0.9) – midsize												
11	Randomized trials	Very serious[a,b,c]	Not serious	Serious[c]	Not serious	None	548	534	-	MD **8.63 lower** (10.88 lower to 6.39 lower)	⊕◯◯◯ Very low	
1.1 T Recovery time to reach TOF 90% (0.9) – large size												
7	Randomized trials	Very serious[a,b,c]	Not serious	Serious[c]	Not serious	None	207	197	-	MD **22.16 lower** (29.87 lower to 14.44 lower)	⊕◯◯◯ Very low	
Length of stay in recovery												
6	Randomized trials	Very serious[b,c,d]	Not serious	Serious[c]	Serious[d]	None	364	370	-	MD **9.91 lower** (15.66 lower to 4.16 lower)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sugammadex × neostigmine	placebo	Relative (95%CI)	Absolute (95%CI)		
Length of stay in recovery – midsize												
3	Randomized trials	Very serious[b,c,d]	Not serious	Serious[c]	Serious[d]	None	176	178	-	MD **15.33 lower** (25.83 lower to 4.83 lower)	⊕◯◯◯ Very low	
Length of stay in recovery – large size												
3	Randomized trials	Very serious[b,c,d]	Not serious	Serious[c]	Serious[d]	None	188	192	-	MD **5.87 lower** (12.65 lower to 0.91 higher)	⊕◯◯◯ Very low	
Nausea												
14	Randomized trials	Very serious[b,c,e]	Not serious	Serious[c]	Not serious	None	131/819 (16.0%)	140/800 (17.5%)	Not estimable	**20 more per 1.000** (from 10 fewer to 50 more)	⊕◯◯◯ Very low	
Nausea – midsize												
12	Randomized trials	Very serious[b,d,e]	Not serious	Not serious	Serious[d]	None	106/738 (14.4%)	120/729 (16.5%)	Not estimable	**20 more per 1.000** (from 10 fewer to 40 more)	⊕◯◯◯ Very low	
Nausea – large size												
2	Randomized trials	Very serious[b,c,e]	Not serious	Serious[c]	Not serious	None	25/81 (30.9%)	20/71 (28.2%)	Not estimable	**10 more per 1.000** (from 400 fewer to 430 more)	⊕◯◯◯ Very low	
Vomit												
12	Randomized trials	Very serious[b,c,d,e]	Not serious	Serious[c]	Serious[d]	None	77/720 (10.7%)	66/620 (10.6%)	Not estimable	**10 more per 1.000** (from 30 fewer to 50 more)	⊕◯◯◯ Very low	
Vomit – midsize												
10	Randomized trials	Very serious[b,c,d,e]	Not serious	Serious[c]	Serious[d]	NONE	66/654 (10.1%)	58/564 (10.3%)	Not estimable	**10 more per 1.000** (from 30 fewer to 50 more)	⊕◯◯◯ Very low	
Vomit – large size												
2	Randomized trials	Very serious[b,c,d,e]	Not serious	Serious[c]	Serious[d]	None	11/66 (16.7%)	8/56 (14.3%)	Not estimable	**10 fewer per 1.000** (from 190 fewer to 170 more)	⊕◯◯◯ Very low	
Hypoxemia												
5	Randomized trials	Very serious[a,b,c,e]	Not serious	Serious[c]	Not serious	None	97/388 (25.0%)	86/395 (21.8%)	**OR 1.21** (0.68 to 2.15)	**34 more per 1.000** (from 59 fewer to 157 more)	⊕◯◯◯ Very low	
Hypoxemia – midsize												
2	Randomized trials	Very serious[a,b,e]	Not serious	Serious[c]	Not serious	None	63/236 (26.7%)	54/236 (22.9%)	**OR 1.25** (0.81 to 1.91)	**42 more per 1.000** (from 35 fewer to 133 more)	⊕◯◯◯ Very low	
Hypoxemia – large size												
3	Randomized trials	Very serious[a,b,c,d,e]	Not serious	Serious[c]	Serious[d]	None	34/152 (22.4%)	32/159 (20.1%)	**OR 1.60** (0.36 to 7.02)	**86 more per 1.000** (from 118 fewer to 438 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sugammadex × neostigmine	placebo	Relative (95%CI)	Absolute (95%CI)		
Hypotensive												
2	Randomized trials	Serious[b,e]	Not serious	Not serious	Not serious	None	4/126 (3.2%)	6/128 (4.7%)	Not estimable	**0 fewer per 1.000** (from 30 fewer to 40 more)	⊕⊕⊕◯ Moderate	
Bradycardia												
10	Randomized trials	Very serious[a,b,e]	Not serious	Not serious	Not serious	None	7/621 (1.1%)	57/563 (10.1%)	**HR 0.14** (0.07 to 0.29)	**86 fewer per 1.000** (from 94 fewer to 71 fewer)	⊕⊕◯◯ Low	
Bradycardia – small size												
2	Randomized trials	Very serious[a,b,e]	Not serious	Not serious	Not serious	None	1/80 (1.3%)	7/80 (8.8%)	**HR 0.13** (0.01 to 1.06)	**76 fewer per 1.000** (from 87 fewer to 5 more)	⊕⊕◯◯ Low	
Bradycardia – midsize												
7	Randomized trials	[a,b,e]	Not serious	Not serious	Not serious	None	6/506 (1.2%)	40/448 (8.9%)	**HR 0.15** (0.07 to 0.33)	**75 fewer per 1.000** (from 83 fewer to 59 fewer)	-	
Bradycardia – large size												
1	Randomized trials	Very serious[a,b,d,e]	Not serious	Not serious	Serious[d]	None	0/35 (0.0%)	10/35 (28.6%)	**HR 0.03** (0.00 to 0.61)	**276 fewer per 1.000** (from 100 fewer to --)	⊕◯◯◯ Very low	
Hypertension												
3	Randomized trials	Very serious[b,d,e]	Not serious	Not serious	Serious[d]	None	15/174 (8.6%)	4/174 (2.3%)	**HR 3.69** (1.27 to 10.75)	**59 more per 1.000** (from 6 more to 198 more)	⊕◯◯◯ Very low	

CI: confidence interval; HR: hazard ratio; MD: mean difference; OR: odds ratio

Explanations

[a]No analysis of intention to treat.

[b]Absence of double blind.

[c]High heterogeneity.

[d]Long confidence interval.

[e]Absence of sample calculation.

APPENDIX IV

MEANING OF TOF (TRAIN OF FOUR)

Neuromuscular blockade can be monitored with different forms of electrostimulation. The TOF consists of performing a sequence of four stimuli at a frequency of 2 Hz with an interval of 10 s between them. The degree of block will be evaluated through the difference in contraction amplitude between the first and fourth sequence of stimuli. It will be considered the existence of muscle block when there is a decrease in the amplitude of response between the stimuli and the existence of anesthetic recovery if all four responses are the same; or according to the T4/T1 ratio.

1. T4/T1>0.7: recovery of diaphragm blockage, but insufficient to prevent aspiration of gastric contents
2. T4/T1>0.8: represents the patient's ability to generate 90% of his tidal volume
3. T4/T1>0.9: desirable and safer value in clinical practice with disappearance of swallowing difficulties

Source: Tardelli MA. Monitoring Neuromuscular Blockade. In: Brazilian Society of Anesthesiology. Distance Education Course in Anesthesiology. Sao Paulo: Office; 2002. p. 177-90.