Protocol

Version 11, 05 October 2023

A blinded randomized study of neostigmine/glycopyrrolate 50 mikrogram/kg or sugammadex 2 mg/kg for reversal of neuromuscular blockade in elderly patients (≥ 75 years).

EU CT number: 2023-504230-21-00
ClinicalTrials.gov number:xxxxx

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Content

Preface

The “A randomized study of neostigmine/glycopyrrolate 50 mikrogr/kg or sugammadex 2 mg/kg for reversal of neuromuscular blockade in elderly patients (≥ 75 years)” trial will be conducted according to this protocol. The trial will be done according to applicable national and international laws, regulations and guidelines. This includes the revised version of the Declaration of Helsinki, European regulations, and the international Good Clinical Practice guidelines. The trial and protocol are developed according with Recommendations for Interventional Trials (SPIRIT) statement. Any substantial changes or amendments to the protocol will be clearly documented and communicated to all relevant parties.

1. List of abbreviations

AE: Adverse event

AR: Adverse reaction

ASA: American Society of Anesthesiologists

CRF: Case report form

ECG: Electrocardiogram

eGFR: estimated glomerular filtration rate

ICF: Informed consent form

IDS: Intubation Difficulty Score

MAP: Mean arterial pressure

NMBA: Neuromuscular blocking agents

PONV: Postoperative nausea and vomiting

PACU: Post Anesthesia Care Unit

SAE: Serious adverse event

SAR: Serious adverse reaction

SUSAR: Suspected unexpected serious adverse event

SMPC: Summary of product characteristics

TOF: Train-of-four

2. Overview

Registry and trial number	XXX
Date of registration	XXX
Sources of monetary or material support	Department of Anesthesia, Centre of Head and Orthopedics, 6013 Rigshospitalet, University of Copenhagen, Denmark
Primary sponsor	Matias Vested
Contact	
Title	A randomized study of neostigmine/glycopyrrolate 50 mikrogr/kg or sugammadex 2 mg/kg for reversal of neuromuscular blockade in elderly patients (≥ 75 years).
Country of recruitment	Denmark
Condition studied	Elderly patients scheduled for elective surgery
Interventions	Sugammadex 2 mg/kg Doses are based on actual body weight
Comparator	Neostigmine/glycopyrrolate 50 mikrogram/kg Doses are based on actual body weight
Inclusion criteria	1) Patients ≥ 75 years old 2) Informed consent 3) Scheduled for robotic assisted laparoscopic surgery under general anesthesia with intubation and use of rocuronium during the entire operation 4) American Society of Anesthesiologists (ASA) physical status classification I to IV 5) Can read and understand Danish
Exclusion criteria	1) Known allergy to rocuronium, sugammadex or neostigmine/glycopyrrolate 2) Neuromuscular disease that may interfere with neuromuscular data 3) Severe renal impairment defined as eGFR < 30 ml/min 4) Indication for rapid sequence induction

	5) Known intestinal or ureter obstruction 6) Known peritonitis
Study type	Interventional Allocation: randomized (1:1) Intervention: sugammadex 2 mg/kg or neostigmine/glycopyrrolate 50 µg/kg Blinding: Medicine will be blinded in 10 mL syringes.
Date of first expected screening	1/6-2023
Target sample size	40
Recruitment status	Waiting
Primary outcomes	Time to TOF > 0.9 (from beginning of administration of reversal agent until TOF > 0.9)
Key secondary outcomes	• Key secondary outcome is sign of residual neuromuscular blockade within 90 minutes after administration of reversal agent defined as a composite (assessed upon arrival at PACU after 20 minutes and after 90 minutes) of either ○ Hand grip strength for 5 seconds or ○ Occurrence of double vision/blurred vision (yes/no) or ○ Ability to track objects with eyes (follow finger of examiner) (yes/no) or ○ Ability to sustain head lift for 5 seconds (yes/no) or ○ Ability to protrude the tongue for 5 seconds (yes/no) or ○ Tongue depressor test (prevent removal of a wooden tongue depressor from between the incisor teeth (yes/no) or ○ Ability to open the eyes for 5 seconds (yes/no) or ○ Ability to smile (yes/no) or ○ Ability to speak (yes/no) or ○ Occurrence of dysphagia/ swallowing impairment assessed by observing difficulties swallowing defined as the ability to drink 20 ml of water (yes/no) or ○ Occurrence of upper airway obstruction or ○ Subjective symptoms of muscle weakness (After each test is completed, patients are questioned by the research assistant about whether the test was difficult to complete or uncomfortable to perform. For example, a patient might

successfully maintain a 5-s eye opening yet note that it was "difficult to keep my eyes open" Subjective symptoms of muscle weakness will be recorded as normal (negative response) or impaired (positive response)

Other secondary outcomes are:

- Occurrence of episodes of desaturation defined as more than 3 minutes with spO2 < 88%
- New cardiac arrythmias (bradycardia or tachycardia defined as atrial fibrillation, atrial flutter, sinus tachycardia (>95 bpm), sinus bradycardia (<45 bpm)) within 180 minutes after administration of reversal agent
- Occurrence of reintubation
- Time from administration of reversal agent to patient is ready to leave the operating room

3. Background

3.1 Elderly patients and residual neuromuscular blockade

Numbers of elderly patients requiring anesthesia and surgery are increasing, and as a group, elderly patients are at high risk of postoperative complications[1]. Aging leads to a progressive impairment of organ function and a decline in physiologic reserve[2] and in the elderly patient population, pharmacodynamics and pharmacokinetics of medications administered during anaesthesia may be influenced by the age-related reduction in cardiac output, liver function and renal function[3] with a large inter-individual variation. Also, the body composition changes with age and elderly have lower total body water and accordingly a relative increase in body fat.

Although the use of neuromuscular blocking agents (NMBAs) to improve surgical condition are still debated and awaiting larger randomized controlled trials, they are routinely administered in the clinical setting during anesthesia both to facilitate tracheal intubation and prevent muscle contractions during surgery which may impair the surgical conditions[4,5]. However, elderly patients administered NMBAs during anesthesia have an increased risk of postoperative residual neuromuscular block which is associated with more frequent episodes of hypoxemia, postoperative pulmonary complications, discomfort and longer hospital length of stay[6].

To prevent postoperative residual block it is strongly recommended to employ objective neuromuscular monitoring perioperatively[2]. Objective monitoring of the depth of the neuromuscular blockade is performed by train-of-four (TOF) stimulation at the ulnar nerve[7]. Neuromuscular monitoring enables the anesthetist to titrate the depth of block and to reverse the block if spontaneous recovery has not occurred upon conclusion of surgery. The dose of reversal agent depends on the depth of the blockade.

It is possible to reverse rocuronium induced neuromuscular blockade with either neostigmine/glycopyrrolate (an acetylcholine esterase inhibitor) or sugammadex (a modified cyclodextrin). However, the optimal choice of reversal agent for rocuronium induced neuromuscular blockade in elderly patients is unknown. There is a need for studies investigating which reversal agent is optimal in elderly patients.

3.2 Neostigmine/glycopyrrolate

Neostigmine/glycopyrrolate, an acetylcholine esterase inhibitor, inhibits the enzyme (acetylcholinesterase) that breaks down acetylcholine at the neuromuscular junction. Neostigmine/glycopyrrolate reverses the effect of rocuronium by an increase in the concentration of acetylcholine at the neuromuscular junction.

Nondepolarizing NMBDs such as rocuronium inhibit neuromuscular transmission primarily by competitively antagonizing or blocking the effect of acetylcholine at the postjunctional nicotinic acetylcholine receptor (nAChR). Binding of rocuronium to the nAChR occurs in a competitive fashion. If larger concentrations of acetylcholine are present at the neuromuscular junction,

acetylcholine will attach to the postsynaptic receptor and facilitate neuromuscular transmission and muscle contraction. Conversely, if larger concentrations of rocuronium are present at the neuromuscular junction, this will prevent muscle contraction.

However, neostigmine has a so-called ceiling effect, i.e. some spontaneous recovery of the block must have occurred before neostigmine/glycopyrrolate is administered. Administration before this time point will not reduce the recovery time[8,9].

The time required to achieve a TOF ratio of 0.90 after neostigmine/glycopyrrolate administration is significantly shorter when a higher TOF count is present. However, a large interindividual variability in reversal times have been reported[10,11].

The maximal effective dose of neostigmine/glycopyrrolate has not been clearly defined, but likely vary in relation to depth of blockade and type of NMBD administered. In general, if deeper levels of neuromuscular blockade are present at the end of surgery (1-2 responses to TOF stimulation), larger doses of anticholinesterases should be given. In these clinical scenarios, maximal doses of neostigmine/glycopyrrolate (70 µg/kg) should be considered. If three to four responses to TOF stimulation are present with observable fade of the fourth response, moderate doses of anticholinesterase should be administered i.e. 40-50 µg/kg of neostigmine/glycopyrrolate. In the elderly patients however, little is known about the optimal dose for reversal and studies in elderly patients suggest that neostigmine/glycopyrrolate is associated with certain side effects such as cardiac arrythmias[12,13].

3.3 Sugammadex

Sugammadex is a modified γ-cyclodextrin, a selective relaxant–binding agent based on an encapsulating principle for inactivation of rocuronium. The complex formation of sugammadex and rocuronium occurs at all levels of neuromuscular blockade (profound through shallow) and results in a more fast-acting pharmacologic reversal when compared with neostigmine/glycopyrrolate.

In contrast to neostigmine/glycopyrrolate, sugammadex can reverse rocuronium blockades within minutes regardless of the depth of neuromuscular blockade by doses of 2.0 to 4.0 mg/kg[14–16].

Sugammadex and the rocuronium-sugammadex complex is primarily eliminated by renal excretion. Because of this sugammadex is not recommended for use in patients with severe renal failure.

3.4 Comparison of neostigmine/glycopyrrolate and sugammadex

After administration of rocuronium during anesthesia it is mandatory to ensure full recovery from neuromuscular blockade before awakening the patient[7]. Residual neuromuscular block is associated with muscle weakness, double vision/blurred vision, impaired pulmonary function and

a higher risk of postoperative respiratory complications[17–19]. Especially elderly patients have a high incidence of residual neuromuscular block[20].

This is ensured either by allowing spontaneous recovery of the blockade or by administering the reversal agents neostigmine/glycopyrrolate or sugammadex[21].

The possible benefit in this trial is to investigate whether neostigmine/glycopyrrolate 50 mikrogr/kg or sugammadex 2 mg/kg provides the fastest reversal of rocuronium induced blockade in the elderly. This may result in different time until reversal of block and different occurrence of side effects and signs and symptoms of residual blockade postoperatively. The results may help to detect the optimal method for reversal of rocuronium induced blockade in elderly patients.

4. Objective and hypotheses

The aim of this study is to determine the time to TOF ≥ 0.9 after either neostigmine/glycopyrrolate 50 mikrogr/kg or sugammadex 2 mg/kg in patients with age ≥ 75 years. The hypothesis of this study is that sugammadex 2 mg/kg provides a faster time to TOF ≥ 0.9 compared to neostigmine/glycopyrrolate 50 mikrogr/kg.

5. Trial design overview

This is a randomized, parallel group, blinded trial comparing neostigmine/glycopyrrolate 50 mikrogr/kg or sugammadex 2 mg/kg for reversal of rocuronium induced blockade in elderly patients (≥ 75 years). Patients will be enrolled at Department of Pediatric and Obstetric Anesthesia, Rigshospitalet, and Department of Anaesthesiology, Bispebjerg Hospital. Forty elderly patients (≥ 75 years) meeting inclusion criteria will be enrolled. The primary outcome is time to TOF ≥ 0.9.

6. Setting and patient population

6.1 Setting

The trial will be conducted at Department of Anaesthesiology, Bispebjerg Hospital, and Department of Pediatric and Obstetric Anesthesia, Rigshospitalet. Both departments have ample elective surgeries and are university hospitals, and therefore acquainted with research within this area.

6.2 Inclusion criteria

The inclusion criteria:

- Age ≥ 75 years
- Scheduled for robotic assisted laparoscopic surgery under general anesthesia with intubation and use of rocuronium for the entire duration of surgery.
- American Society of Anesthesiologists physical status classification (ASA) I to IV
- Informed consent (see appendix 1)

- Read and understand Danish

These inclusion criteria have been chosen because they make sure, that it is ethically correct to perform the trial and because similar criteria have been used in previous studies conducted within this field. They are broad to make sure as many patients as possible can be included.

6.3 Exclusion criteria

The exclusion criteria:

- Neuromuscular disease
- Known allergy to rocuronium, neostigmine/glycopyrrolate or sugammadex
- Severe renal impairment defined as eGFR < 30 ml/min
- Indication for rapid sequence induction
- Known intestinal or ureter obstruction
- Known peritonitis

Neuromuscular diseases may affect the monitoring of the effect of both rocuronium and reversal agents and may therefore cause imprecise data on the level of block and hence make the data unusable.

7. Interventions

7.1 Interventions

Study drugs

The study drugs are neostigmine/glycopyrrolate (neostigmine/glycopyrrolate "Meda") and sugammadex (Bridion "MSD"). The patients will either receive a bolus of neostigmine/glycopyrrolate 50 mikrogr+10 mikrogr/kg or sugammadex 2 mg/kg for reversal of the neuromuscular blockade upon conclusion of anaesthesia defined as after removal of the laparoscopic instruments. Doses are based on actual body weight rounded to nearest 10 mg for sugammadex and nearest 0.1 mg for neostigmine/glycopyrrolate. Glycopyrrolate is added in the ampoule by the manufacturer: 0.5 mg per 2.5 mg of neostigmine/glycopyrrolate.

A separate investigator will prepare the dose, based on the above-mentioned dosing schedule. To make the syringes similar, saline will be added to the syringes to a total volume of 10 mL. The separate investigator will calculate the dose and prepare syringes in a closed room. The syringes will be passed to another investigator blinded to the content of the syringes. This investigator will bring the syringe to the operation room and passed to an anesthesiologist or an anesthetist nurse. They will administer the drug as a bolus over 5 seconds in an intravenous catheter.

Patients can take their usual medicine before and after surgery according to the anaesthesia plan scheduled by the anaesthesiologist.

7.2 Monitoring

Preoperatively

Assessment of muscle strength:

Preoperatively, before arriving to the operating room, an investigator will assess the patients´ muscle strength. After careful instruction by the investigator the patient will perform

- Hand grip strength assessed by a dynamometer
- Chair stand test five times [22–24]
    - To test the ability to rise from a chair (termed the chairstand), a straight-backed chair is placed next to a wall; patients will be asked to fold their arms across their chest and to stand up from the chair one time. If successful, patients will be asked to stand up and sit down five times as quickly as possible and are timed from the initial sitting-position to the final standing position at the end of the fifth stand.

Intraoperatively

All patients will be monitored with ECG, non-invasive blood pressure and oxygen saturation. To make sure the temperature centrally and peripheral is kept above 35 °C and 32 °C, according to guidelines (GCRP Fuchs-Buder), a forced air patient warming system will be placed on the patient and the arm will be covered in sterile surgical covering. The temperature will be monitored with sensors in nose cavity, gullet, rectum or bladder and on the thenar eminence with TOF Watch SX monitor.

All patients will have neuromuscular monitoring performed with TOF-Watch SX monitor connected to a computer for collection of neuromuscular data (Version 2.5 INT 2007, Organon, The Netherlands). The monitoring will be done according to international guidelines[25]. TOF-Watch SX will be placed on the arm, where there is the least monitoring equipment. Initially, the skin will be cleansed and rubbed with an abrasive. Small electrodes will be used and placed on the wrist over the ulnar nerve. The acceleration transducer will be placed on the thumb and attached in the associated hand adaptor. When the patient is adequately anesthetized, we will start the TOF Watch SX monitor and give two train-of-four (TOF) nerve stimulations followed by a tetanic stimulation with 50 Hz for 5 seconds. Then we will calibrate the TOF Watch SX monitor with the CAL2 button and start the TOF mode and measure the TOF (2 Hz for 1.5 seconds) each 15 sec. After securing a stable signal with less than 5% deviation for two minutes rocuronium 0.6 mg/kg will be injected.

The arm will be fixed to the armrest by bandages. An intravenous catheter will when possible be placed in the opposite hand.

Postoperatively

Patients will be observed at the post-anesthetic care unit (PACU) for at least 3 hours.

Postoperatively patients will receive a standardized regimen according to local guidelines regarding:

- Pain treatment
- Treatment of nausea and vomiting
- Administration of fluids (crystalloids)
- Administration of antibiotics

Oxygen will be administered targeting a saturation of 94-98% (or 88-92% in case of COPD or BMI>=40).

If saturation is < 90% > 5 minutes patients will be placed in semi sitting position (30 degrees) and receive continuous positive airway pressure (CPAP).

Immediately upon arrival at the PACU a blinded investigator will assess signs and symptoms of residual block[26]. The assessment will be repeated after 20 minutes and after 90 minutes.

Sign of residual muscular blockade are defined as either[26]

- Hand grip strength for 5 seconds or
- Occurrence of double vision/blurred vision (yes/no) or
- Ability to track objects with eyes (follow finger of examiner) (yes/no) or
- Ability to sustain head lift for 5 seconds (yes/no) or
- Ability to protrude the tongue for 5 seconds (yes/no) or
- Tongue depressor test (prevent removal of a wooden tongue depressor from between the incisor teeth (yes/no) or
- Ability to open the eyes for 5 seconds (yes/no) or
- Ability to smile (yes/no) or
- Ability to speak (yes/no) or
- Occurrence of dysphagia/ swallowing impairment assessed by observing difficulties swallowing defined as the ability to drink 20 ml of water (yes/no) or
- Occurrence of upper airway obstruction or
- Subjective symptoms of muscle weakness (After each test is completed, patients are questioned by the research assistant about whether the test was difficult to complete or uncomfortable to perform. For example, a patient might successfully maintain a 5-s eye opening yet note that it was “difficult

to keep my eyes open" Subjective symptoms of muscle weakness will be recorded as normal (negative response) or impaired (positive response)

As a standard during the PACU stay blood pressure, pulse and oxygen saturation will be monitored continuously. In addition, the following will be registered:

- Occurrence of episodes of desaturation defined as more than 3 minutes with spO2 < 88%.
- New cardiac arrythmias (bradycardia or tachycardia defined as atrial fibrillation, atrial flutter, sinus tachycardia, sinus bradycardia) within 90 minutes after administration of reversal agent
- Occurrence of upper airway obstruction
- Occurrence of reintubation

Before discharge from the PACU an arterial blood gas analysis will be drawn.

In case of reoperation information regarding allocation can be reached either at the allocation-chart or by contacting the local investigator by phone 24/7. Phone number, name of investigator and placement of allocation-chart will be noted in the patient record.

7.3 Concomitant treatment

7.3.1 Treatment values intraoperatively

Blood pressure: Aiming at a mean arterial pressure (MAP) of 65 mmHg and a systolic blood pressure above 90.

Neuromuscular monitoring continues until TOF ≥ 0.90 and stable over 2 min. In case the depth of neuromuscular blockade is within the range from TOF count of 2 to a TOF ratio < 0.60 at the end of operation the NMB is reversed with neostigmine/glycopyrrolate or sugammadex according to allocation. Subsequently, the patient is awakened and taken to the recovery room.

In case TOF ratio is > 0.6 upon conclusion of anaesthesia no reversal agent will be administered.

In case TOF count is ≤ 1 upon conclusion of anaesthesia the attending anaesthesiologist can

either

- decide to await reappearance of a TOF count of 2 and subsequently administer the study drug (time from ready to administer the reversal agent until reappearance of TOF count of 2 will be registered)

or

- administer sugammadex.

7.3.2 Anesthesia

General anesthesia is induced with propofol 1 – 2 mg/kg as needed to obtain loss of eyelash reflex. Tracheal intubation is performed after administration of rocuronium 0.6 mg/kg when TOF count is 0.

Tracheal intubation can be performed either with a laryngoscope or video laryngoscope.

Anesthesia will be maintained according to local guidelines with an infusion of propofol of approximately 5 mg/kg/hour and remifentanil approximately 0.25–0.5 µg/kg/min.

Supplemental doses of rocuronium will be administered according to the discretion of the attending anaesthesiologist either as bolus or infusion aiming at a TOF count of 1-2.

A central venous catheter (CVK) and an arterial line may be placed either before or after induction of anesthesia according to the discretion of the anesthetist.

Vasopressors (norepinephrine, ephedrine, or phenylephrine) are administered at the discretion of the attending anesthesiologist.

8. Sample size and recruitment strategies

8.1 Sample size

The sample size calculation is based on our primary hypothesis. A previous study has found that time to TOF 90% after administration of sugammadex 2 mg/kg upon reappearance of T2 was approximately 4 minutes with a standard deviation of 2 minutes[27]. A Cochrane review has found that in adults time to TOF 90% after administration of 0.05 mg/kg of neostigmine/glycopyrrolate upon reappearance of T2 was approximately 12 minutes with a standard deviation of 2.5 min[28]. With a sample of 20 patients in each group we are able to detect this difference with a power of 90% and a 5% risk of type 1 error. A total of 40 patients must be included and recruitment will continue until 40 patients has been enrolled, received one of the interventions and the primary outcome has been assessed. Up to 70 patients can be included.

8.2 Recruitment strategies

Patients are recruited among those referred to the Department of Anaesthesiology, Bispebjerg Hospital, and Department of Pediatric and Obstetric Anesthesia, Rigshospitalet, who meet inclusion criteria and who have no exclusion criteria.

The principal investigator is in charge of informing the patients and obtaining informed consent forms. If the principal investigator is not able to interview a patient another investigator, with GCP experience and knowledge of anesthesia and the protocol, can interview and include the patient.

The anesthesiologist in charge of treatment, will go through the schedule for elective surgery and screen for potential candidates to the project. The anesthesiologist will then inform the principal investigator of any potential candidates. The principal investigator will then contact the patient at the hospital during the pre-anesthetic interview. Patients will be informed about the project, preferably 1 to 14 days before planned operation, at least 24 hours before operation. This will happen in an undisturbed room. The patient will be offered the possibility of being accompanied by a next of kin. The patient will receive information orally and written. The patient is informed, that it is voluntary to participate, and he/she has the right to disclaim consent without affecting further treatment. Patients will be offered at least 24 hours to consider giving consent. Patients may however, after receiving orally and written information give consent immediately. If patients accept to be included in the project, they need to fill out an informed consent form. This will preferably be obtained before patients arrive to the operation ward, and thereby avoid putting the patient in a situation where a decision about participating in the trial must be made in a stress-full environment at the operation ward.

All patients will be contacted 3 days postoperatively to be asked if any adverse events (see 12.3.2) have happened.

Patients will be screened until target population of 40 patients has been achieved.

8.3. Trial timeline

	Pre-trial	2 moths	4 months	6 months	8 months	10 months	12 months	14 months
Development of protocol and modifications								
Ethical approval								
Registration with Danish Medicine Agency								
Trial registration								
Inclusion of patients		*June 2023*						
GCP monitoring								
Data analysis								
Manuscript writing								
Publication								*December 2024*

Inclusion of approximately 2 patients per week is expected corresponding to a duration of approximately 6-8 months. Inclusion: Planned to go on in the period from June 2023 through September 2024. Inclusion of patients will be stopped when the primary endpoint has been assessed in 40 patients or the maximum of 70 patients has been included. The trial will be counted as concluded when the last patient has registered with the primary endpoint.

Data analysis and reporting: from September 2024 through December 2024.

The trial will be considered as having started on the date when there is a signed declaration of consent from the first patient, who will thereby be considered as included. Conclusion of the study is when the last patient has been evaluated considering the primary outcome and has had their 3-day follow-up call.

9. Outcome

9.1 Primary outcome

The primary outcome is the time to TOF ≥ 0.9 after administration of either sugammadex or neostigmine/glycopyrrolate defined as start of injection until appearance of the first TOF ratio ≥ 0.9 followed by a stable signal with a TOF ratio ≥ 0.9 for at least two minutes.

Time to TOF ≥ 0.9 has been chosen as the primary outcome because it is clinically relevant to examine whether administration of neostigmine/glycopyrrolate or sugammadex provides the fastest reversal of rocuronium-induced neuromuscular blockade in patients above 75 years of age. This patient population is at high risk of severe respiratory complications if residual blockade is present. Therefore, it is clinically relevant to investigate which of the two reversal agents that is associated with the fastest reversal.

9.2 Secondary outcome

- Key secondary outcome[26] is sign of residual muscular blockade within 90 minutes after administration of reversal agent defined as a composite (assessed upon arrival at PACU after 20 minutes and after 90 minutes) of either
    - Hand grip strength for 5 seconds or
    - Occurrence of double vision/blurred vision (yes/no) or
    - Ability to track objects with eyes (follow finger of examiner) (yes/no) or
    - Ability to sustain head lift for 5 seconds (yes/no) or
    - Ability to protrude the tongue for 5 seconds (yes/no) or
    - Tongue depressor test (prevent removal of a wooden tongue depressor from between the incisor teeth (yes/no) or
    - Ability to open the eyes for 5 seconds (yes/no) or
    - Ability to smile (yes/no) or
    - Ability to speak (yes/no) or
    - Occurrence of dysphagia/ swallowing impairment assessed by observing difficulties swallowing defined as the ability to drink 20 ml of water (yes/no) or
    - Occurrence of upper airway obstruction or
    - Subjective symptoms of muscle weakness (After each test is completed, patients are questioned by the research assistant about whether the test was difficult to complete or uncomfortable to perform. For example, a patient might successfully maintain a 5-s eye opening yet note that it was “difficult to keep my eyes open” Subjective symptoms of muscle weakness will be recorded as normal (negative response) or impaired (positive response)

Other secondary outcomes are:

- Occurrence of episodes of desaturation defined as more than 3 minutes with spO2 < 88%.
- New cardiac arrythmias (bradycardia or tachycardia defined as atrial fibrillation, atrial flutter, sinus tachycardia (>95 bpm), sinus bradycardia (<45 bpm)) within 180 minutes after administration of reversal agent
- Occurrence of reintubation
- Time from administration of reversal agent to patient is ready to leave the operating room

10. Assignment of interventions

10.1 Allocation

Patients will be allocated randomly at a ratio of 1:1 to receive either 2 mg/kg sugammadex or 50 µg/kg neostigmine/glycopyrrolate. Randomization will be done at the day of operation after written informed consent is obtained. An independent investigator will allocate patients in the two groups by using a computerized random number generator in REDCap. In REDCap patients also receive a number, which pseudo anonymizes data. To decrypt data a reversal key is needed. This will be made in a Microsoft Excel sheet and will be stored on a secure drive. Only people involved in the study and with the right authority will be granted access to the drive. This will be controlled during the study.

10.2 Blinding

Intervention medicine is prepared in the medicine room before the operation. This is done under double control by the investigator who also performed the randomization. The project medicine, either sugammadex or neostigmine/glycopyrrolate, will be prepared in a syringe. The dose will be mixed with saline to a total of 10 mL to secure blinding. A label with patient's initials, randomization number and "sugammadex or neostigmine/glycopyrrolate" is put on the syringe. It will be noted on a sheet which medicine each patient receives, batch number, expiration date and the initials of the investigator will be noted on a sheet. After conclusion of preparation the sheet will be placed in the accompanying envelope, which is sealed and placed in a folder together with the informed consent. The folder is stored in a locked room where only investigators of the study have access. The envelope must only be opened, if it is considered strictly necessary to know which group the patient belongs to with respect to further treatment. This will happen after agreement with the investigator responsible for the trial. Motivation for broken seal shall be included in the Case Report Form (CRF).

The syringe will be handed over to an investigator who will bring it to the OR, where an anesthetist or nurse anesthetist will administer the reversal agent (neostigmine/glycopyrrolate or sugammadex).

The patient will at no time during hospitalization and 3-day follow up be informed about treatment group allocation. The patient may however be informed of this upon conclusion of data collection.
The surgeon will be blinded to treatment group allocation during the operation.
The anesthesia personnel will be blinded to treatment group allocation during reversal of the neuromuscular blockade, but after gathering the data, they will be unblinded.
The investigator controlling the TOF Watch will be unblinded during the operation.
Surgical personnel will be blinded to treatment group allocation during the operation.

The secondary outcomes will be assessed by an investigator without access to treatment group allocation.

11. Data collection and management

11.1 Data collection

Data will be collected on a separate computer with TOF Watch XS monitor software and noted on a CRF during the surgery. The collected NMB data will be stored on a closed drive after being pseudo anonymized. A transformation key will be made and stored in a separate secure place. All information for this study will be gathered from CRF, TOF Watch XS monitor software and electronical medical journals.

11.1.1 Study related variables

Patient ID
Inclusion criteria
Exclusion criteria
Informed consent form

11.1.2 Preoperative variables

Age
Sex
Height
Weight
ASA
Co-morbidity
Medicine intake

Chair stand test five times

All patients will be assessed for frailty using the FRAIL Scale[29]

- *Fatigue*, defined as subjective feeling of tiredness over past 4 weeks “most or all” of the time

- *Resistance*, is scored positive if the patient has difficulty climbing 10 steps without an assist device or stopping to rest
- *Ambulation*, is scored positive if the patient has difficulty walking 2 blocks independently
- *Illnesses*, is scored positive if the patient has 5 or more co-morbidities: hypertension, diabetes, cancer, asthma, chronic lung disease, heart attack, congestive heart failure, angina, arthritis, stroke, and kidney disease.
- *Loss of weight* is scored positive if the patient has lost more than 5% of bodyweight over past year

A score of 1 is assigned to each positive domain. A score of 0 is categorized as robust, 1–2 as prefrail, and ≥ 3 as frail.

11.1.3 Intraoperative variables

- Duration of anesthesia (induction to ready to leave the OR)
- Duration of operation (incision to last suture)
- Time of administration of neostigmine/glycopyrrolate or sugammadex
- Level of NMB upon administration of reversal agent
- Time to TOF 0
- Time of intubation

11.1.4 Outcome variables

- Time to TOF ≥ 0.9
- Occurrence of episodes of desaturation defined as more than 3 minutes with spO2 < 88%.
- New cardiac arrythmias (bradycardia or tachycardia defined as atrial fibrillation, atrial flutter, sinus tachycardia, sinus bradycardia) within 90 minutes after administration of reversal agent
- Occurrence of reintubation
- Time from administration of reversal agent to patient is ready to leave the operating room
- Sign of residual muscular blockade within 90 minutes after administration of reversal agent defined (assessed upon arrival at PACU after 30 minutes and after 90 minutes) as either
    - Hand grip strength for 5 seconds or
    - Occurrence of double vision/blurred vision (yes/no) or
    - Ability to track objects with eyes (follow finger of examiner) (yes/no) or
    - Ability to sustain head lift for 5 seconds (yes/no) or
    - Ability to protrude the tongue for 5 seconds (yes/no) or
    - Tongue depressor test (prevent removal of a wooden tongue depressor from between the incisor teeth (yes/no) or
    - Ability to open the eyes for 5 seconds (yes/no) or
    - Ability to lift one arm to the opposite shoulder (yes/no) or

- Occurrence of dysphagia/ swallowing impairment assessed by observing difficulties swallowing defined as the ability to drink 20 ml of water (yes/no) or
- Ability to speek or
- Occurrence of upper airway obstruction or
- Subjective symptoms of muscle weakness (After each test was completed, patients were questioned by the research assistant about whether the test was difficult to complete or uncomfortable to perform. For example, a patient might successfully maintain a 5-s eye opening yet note that it was “difficult
  to keep my eyes open” Subjective symptoms of muscle weakness will be recorded as normal (negative response) or impaired (positive response)

11.2 Data management

The data from the CRF and from TOF Watch XS monitor software will be added to REDCap, which is a legal and secure web application for storing research data. The data collected in this trial will be secured with two-step access. CRF will be stored in a trial master file along with all the applications, approvals and trial relevant documents. The trial master file will be stored in locked premises. The ICFs will be stored in a locked drawer in a separate office.

Upon granting of informed consent, principal investigator, sponsor, a representative of sponsor or third parties are authorized access to the patients´ journal to find information regarding the patients´ health conditions that are relevant for the conduction of the trial.

Primary investigator will arrange for data collection and storage of CRFs and ICFs in locked premises. Data will be stored for 5 years after conclusion of the trial. The information about the patients’ health conditions, other purely private circumstances and other information that arises in connection with the trial are covered by the obligation of confidentiality. The information concerning the patients is protected by databeskyttelsesforordningen og databeskyttelsesloven.

11.3 Statistical analysis

Eligible patients and excluded patients will be registered at a screening list.

Data from all randomized patients, who receive the intervention and with at least primary outcome, will be included in the intention-to-treat analysis.

Patients, included in the intention-to-treat analysis, but who are categorized as major violation (defined as use of sevoflurane, succinylcholine, aminoglycosides, magnesium), will be excluded from the per-protocol analysis.

Normally distributed variables will be reported by means and standard deviations; variables that are not normally distributed will be reported by medians and interquartile ranges. Student´s t-test is used to compare normally distributed data and Mann-Whitney test to compare not normally distributed data. X^2-test or Fisher´s exact test will be used for frequencies when comparing the

two groups. Ninety-five percent confidence intervals will be used for quantifying differences. A $p < .05$ is considered statistically significant.

Data will also be reported separately for patients ≥ 80 years and 75-80 years.

The data analysis will be blinded. The investigator analyzing data will be blinded towards treatment group allocation. The treatment groups will be named A and B and after completion of the data analysis the treatment group allocation will be unblinded.

12. Ethical considerations

12.1 Registrations and approvals

The trial will be done according to the protocol. Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by principal investigator and sponsor and approved by the Scientific Ethics Committees prior to implementation and notified to the health authorities in accordance with local regulations.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be agreed upon by principal investigator and sponsor and will be documented in a memorandum.

The trial will be reported to the Scientific Ethics Committees, Danish Medicines Agency and Videnscenter for Dataanmeldelser. The patients in the trial are assured access to receive further information about the trial through the principal investigator, who as contact person is referred to in the patient information. The “Dine rettigheder som forsøgsperson i forsøg med medicin (Rights of Trial Subjects)” published by the Scientific Ethics Committee will be provided.

General procedures for quality control and quality assurance will be followed, according to ICH GCP guidelines. Data will be monitored by the GCP unit. Upon granting of informed consent, authorization will be obtained from the patients for third parties to be able to have access to information about the patient´s health condition. The investigator will thus allow the GCP unit or the Danish Medicines Agency direct access to source data/documents with monitoring, auditing and/or inspection.

Receipt control of sugammadex and neostigmine/robinul will be done according to the departmental standards for handling and storage of medicine as both products are standard medicine at the department. Both sugammadex and neostigmine/robinul are stored in the medicine room where temperature is controlled.

At the end of the trial, investigator and sponsor will inform the Scientific Ethics Committee and the Danish Medicines Agency of this within 90 days. The trial will be registered in an international database (www.clinicaltrials.gov), before the recruitment of patients is started.

12.2 General considerations

The number of elderly is increasing and elderly people reach a higher age healthier than previously. With increasing age the body and the organ functions change, why it is important to examine the effect of some of the medication used daily during anesthesia.

Neostigmine/glycopyrrolate and sugammadex are both able to reliably reverse a rocuronium-induced neuromuscular blockade. Anesthesia and surgery will follow guidelines apart from the use of the reversal agent. We think that it is justifiable that information about the use of project-medicine will be stored in the RedCap Database. There is an option to get access to the Red Cap Database in an emergency situation. If necessary, the investigator can at any time unblind from a medical judgement independent of sponsor. This can be done through the Red Cap database. Unblinding of the included patients will be done after the last day-3 follow-up.

The possible benefit in this trial is to investigate whether sugammadex or neostigmine/glycopyrrolate provides the fastest reversal of the rocuronium-induced neuromuscular blockade in the elderly and if there is a difference in side-effects between the two reversal agents. The results will help the clinician to make a rational choice of reversal agent in the elderly based on the time to reversal of neuromuscular blockade and occurrence of side effects. There are no personal benefits for the individual patients.

Informed consent will be obtained before the patients arrive to the operation ward. We thereby wish to avoid having the patient to decide about participating in the trial at the operation ward since patients arriving at the operation ward may perceive this as a stressful environment. The inclusion and exclusion criteria used will ensure that we only investigate patients who will be able to tolerate being treated according to the two strategies. Intervention with respect to possible complications from this, are not changed either.

12.3 Consent

Information about the trial will be done by an investigator trained in the protocol. The patient will receive information orally and written. Patients will then be able to have an informed discussion with the investigator. Informed consents will then be gathered, and the patient will be offered the possibility of receiving a copy of the ICF.

12.4 Risk and safety issues

Both sugammadex and neostigmine/glycopyrrolate can affect the cardiovascular system and lead to hypotension and bradycardia or tachycardia, why strict monitoring will be done according to 7.2. If cardiovascular side effects occur, they will be handled according to local guidelines.

More elderly people will need operation at some point. During all operations there is a risk of awareness and patients in this study will be carefully sedated and they will be monitored closely with TOF monitoring until they have recovered completely from neuromuscular block.

12.4.1 Definitions

- Adverse event; any untoward medical occurrence in a subject to whom a medicinal product is administered, and which does not necessarily have a causal relationship with this treatment.
- Serious adverse event; any untoward medical occurrence that at any dose requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death.
- Unexpected serious adverse reaction; a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information.

12.4.2 Side effects

Sugammadex: According to the product summary side effects are:

- Common (1-10%): Bradycardia, tachycardia, coughing, hypotension.
- Not common (0,1-1%): Allergic reaction, consciousness during anesthesia (awareness).
- Incidence unknown: cardiac arrest

Neostigmine/glycopyrrolate: According to the product summary side effects are:

- Common (>10%): Bradycardia, tachycardia, dry mouth, increased peristalsis, excessive salivation, tiredness, reduced sweating.
- Not common (0.1-1%): Accomodation difficulties, urinary difficulties.
- Seldom (0.01-0.1%): 2. Degree AV-block, cardiac arrest, anaphylaxis, prolonged QT interval, hypotension.

12.4.3 Adverse events

In this trial a list of adverse events of special interest has been made. Other AE's and AR's will not be reported as the safety profile is well known and well described in the SMPC's:

1) Bradycardia, tachycardia, AV-block, prolonged QT interval
2) Excessive salivation, increased peristalsis or reduced sweating
3) Accomodation difficulties
4) Urinary difficulties
5) Allergic reaction or anaphylaxis

They will be controlled and monitored by a follow-up call 3 days after operation.

Patients with AEs/SAEs will be followed by investigator until solved.

12.4.4 Reporting of adverse events

All SAE´s and SAR´s will be reported to sponsor within 24 hours of discovery. If the serious adverse reaction is not indicated in the product information, it is considered to be unexpected. Both investigator and sponsor (or sponsor-investigator) will assess the causality. The sponsor must not override the investigator's evaluation, so reports must be submitted even though the sponsor does not agree with the investigator. The Sponsor will report SUSARs to the Danish Medicines Agency and Research Ethics Committee within 7 days for those that are fatal or life-threatening. All other SUSARs will be reported no later than 15 days from the time when the sponsor is informed. Sponsor will be registered in the EudraVigilance system, as this is a requirement for SUSAR reporting.
Once a year, the Sponsor will submit a list of all SARs in the reporting period and a report on patient safety to the Danish Medicines Agency and Ethics committee and Clinical Trials Information System (CTIS).
The Sponsor will notify the Danish Medicines Agency and Ethics Committee when the trial has completed (no later than 90 days thereafter) and if earlier than planned, within 15 days with the reasons for stopping the trial. In addition, the results including endpoint, SAEs and SARs will be reported on EudraCT not later than 1 year after last patient last visit.

12.4.5 Timeline

Patients will receive either sugammadex or neostigmine/glycopyrrolate for reversal of the neuromuscular blockade upon conclusion of anesthesia and patients will be awakened when complete recovery of the NMB is established (TOF ratio above 0.9 for two minutes).

End of trial is defined as the time when the last included patient has completed the follow up call three days after surgery.

12.4.6 Suspected unexpected serious adverse reaction

Suspected unexpected serious adverse reactions (SUSARs) are SAEs, which are expected to be a side effect of the trial drug, where the event has not been noted as part of the side effects of the drug. The patient experiencing the SUSAR will be unblinded and the incidence will be reported to Danish Medicine Agency. The expectedness assessment will be done by sponsor (whether SAR or SUSAR).

12.4.7 Reporting

When finished with the study either sponsor or principal investigator will submit a list of all adverse events registered during the trial to Danish Medicines Agency (See section 12.1).

12.4.8 Insurance

The patients in the present trial are covered by the patient insurance, covering all treated patients at the trial site at Rigshospitalet/Bispebjerg Hospital in Copenhagen in the event of a trial-related injury or death occurring. This is in accordance with the applicable law and with the CPMP Note for Guidance on Good Clinical Practices (CPMP/ICH/135/95) of July 17th, 1996.

13. Publication

The results, positive, negative or inconclusive, will be submitted for publication in an international, English-language journal. Authorship will occur in accordance with international Committee of Medical Journal Editors' rules (the Vancouver Group). Data belong to the patients and will be collected and stored according to this protocol. The right to data and know-how that emerges in connection with the trial will belong to investigators and the Department of Anaesthesia, Centre of Head and Orthopaedics, 6013 Rigshospitalet, University of Copenhagen, Denmark.

The trial will be registered on www.clinicaltrials.gov and in the EudraCT database. Data describing the trial design, safety and efficacy will be reported in the EudraCT database within 1 year after completion of the trial.

The trial results will be submitted to the Clinical Trials Information System (CTIS) portal and subsequently, data will be published on clinicaltrialsregister.eu.

Tentative author list is:

MV (first author) - other study authors fulfilling the Vancouver criteria.

We intend to include site investigators as co-authors, if they enroll and randomize at least 3 patients.

14. Economy

Matias Vested and Lars S Rasmussen have taken initiative to this study.
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