Neuromuscular blocking agents in the elderly

Protocol

An observational study of rocuronium 0.6 mg/kg comparing onset time, duration of action and effect on intubating conditions in younger (18 – 40 years) and elderly patients (> 80 years)

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Background

The number of elderly patients (>80 years) is increasing and a large proportion of these patients will require surgery and anesthesia within the next decades[1]. Elderly patients are at higher risk of major morbidity and mortality[2] and are characterized by a reduction in cardiac output, liver function and renal function. These physiological changes influence pharmacodynamics and pharmacokinetics of drugs administered during anesthesia as for example neuromuscular blocking agents (NMBA).

During anesthesia NMBAs are used to facilitate tracheal intubation, establish muscle relaxation and suppress reflexes during surgery[3–5]. Elderly patients are more sensitive towards muscle relaxants. In addition studies have reported prolonged duration of NMBAs[6–8] and an observational study found that elderly patients are more prone to experience residual neuromuscular blockade in the post anesthesia care unit[9]. However, most studies have been conducted in elderly below 80 years[7,10].

It is unknown if there are differences in onset times of NMBAs e.g. rocuronium, mivacurium and cisatracurium between younger patients and elderly. Onset time for NMBAs in the elderly is of importance since it may influence intubating conditions, especially during rapid sequence induction. For example it is unknown in the elderly if an increased dose of NMBA reduces the onset time. There remains a need for studies investigating the optimal dose for facilitating intubation in the elderly, both during rapid sequence induction and during elective procedures.

The aim of this study is to determine the onset time, duration of action and effect on intubating conditions for rocuronium 0.6 mg/kg in patients aged 18-40 years and in patients with age > 80 years. The hypothesis of this study is that rocuronium administered in elderly patients (>80 years) has a longer onset in the elderly compared to younger patients.

Method:

Design:

Observational clinical study

Outcomes:

The primary end point is onset time, defined as the time from the end of rocuronium injection to Train-of-four (TOF) count of 0 monitored by acceleromyography.

The secondary endpoints are intubating conditions rated by an intubating difficulty scale[11] after 90 seconds and duration of action, defined as time from end of rocuronium injection to reappearance of TOF ratio > 0.9.

The pharmacodynamic data obtained are: time to reappearance of the T1, time to T1 recovery to 25% (of the final T1), and time to TOF ratio 0.90

Number of patients: 32 patients (16 in each group):

Group young: 16 patients receiving rocuronium 0.6 mg/kg

Group elderly: 16 patients receiving rocuronium 0.6 mg/kg

Doses are based on ideal body weight, calculated as height (cm) minus 105 for women and height (cm) minus 100 for men.

Inclusion criteria:

Patients > 18 years old

Informed consent

Scheduled for elective surgery (>1 hour) under general anaesthesia with intubation and use of rocuronium

American Society of Anesthesiologists (ASA) physical status classification I to III

Can read and understand Danish

Exclusion criteria:

Known allergy to rocuronium

Neuromuscular disease that may interfere with neuromuscular data

Indication for rapid sequence induction

End of study:

When 32 patients have been evaluated considering the primary endpoint the study is concluded.

Pre-operative assessment:

In the Case Report Form (CRF) the following baseline data is noted:

Age

Sex

Weight

Height

BMI

ASA group (I-IV)

Co-morbidity

Perioperative treatment:

Monitoring:

The patient will be monitored with ECG, noninvasive blood pressure, oxygen saturation, and temperature sensors in nose cavity or bladder. Neuromuscular monitoring will be performed with TOF-Watch SX 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[13]. TOF-Watch SX will be placed on the arm, where there is the least monitoring in general. Initially, the skin will be shaved and cleansed and rubbed with an abrasive. Small ECG electrodes will be used. They will be 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 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 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 we will inject rocuronium. When TOF = 0 we will measure the PTC for every 3-4 minutes.

An intravenous catheter will be placed in the opposite hand.

Anesthesia:

General anesthesia comprises induction with propofol 1-2 mg/kg and fentanyl 1.5-3.0 mcg/kg. Tracheal intubation is performed 90 seconds after administration of rocuronium 0.6 mg/kg. Anesthesia will be maintained with propofol approximately 5 mg/kg/hour and remifentanil 0.25-0.5 mcg/kg/min and adjusted according to depth of anesthesia.

Treatment values:

Blood pressure: Mean arterial pressure (MAP) max. 30 % difference from baseline.

Neuromuscular monitoring continues until TOF ≥ 0.90 and stable over 2 min. In case of TOF < 0.90 at the end of surgery the NMB is reversed with neostigmine or sugammadex according to guidelines at the department. Subsequently, the patient is awakened and taken to the recovery room.

Intubating conditions:

Intubating conditions will be assessed 90 seconds after end of injection of rocuronium 0.6 mg/kg employing the Intubating Difficulty Scale. The scale comprises seven items:

N1-The number of supplementary attempts, an attempt defined as one advancement of the tube in the direction of the glottis during direct laryngoscopy or one like advancement of the tube in the case of a blind intubation trial.

N2-The number of supplementary operators; N2represents the number of additional persons directly attempting (i.e., not assisting) intubation.

N3-The number of alternative techniques used. For example, changing from an oral intubation to blind nasotracheal intubation or from a curved blade to straight blade increases N3by 1 point. The various techniques used should be noted in chronological order, so that subsequent identification of techniques ineffective in a particular case (or series) may be undertaken.

N4-Glottic exposure as defined by the Cormack grade [4] minus one; grade I (N4= 0) on this scale corresponds to complete visualization of the vocal cords, grade II (N4= 1) to visualization of the inferior portion of the glottis, grade III (N4= 2) to visualization of only the epiglottis, and grade IV (N4= 3) to a nonvisualized epiglottis. Glottic exposure is evaluated during the first attempt by the first operator. In case of successful intubation after blind nasotracheal intubation, N4= 0. If the blind attempt(s) fail, glottic exposure is evaluated during the first subsequent alternative visualized laryngoscopic attempt.

N5-The lifting force applied during laryngoscopy; N5= 0 if little effort is necessary, and N5= 1 if subjectively increased lifting force is necessary. This notion is based on the operator's impression that an abnormal amount of force was used compared with routine practice.

N6-The necessity of applied external laryngeal pressure for optimized the glottic exposure; N6= 0 if no external pressure is applied. N6= 1 if external laryngeal pressure is necessary. Application of the Sellick Maneuver is intended to inhibit aspiration of gastric contents and does not alter the score.

N7-Position of vocal cords; N7= 0 if vocal cords are in abduction. N7= 1 if the vocal cords are in abduction, presenting an impediment to tube passage. If the vocal cords are not visualized, N7= 0 by default.

Positioning:

The patient will be positioned with the arm with neuromuscular monitoring equipment in abducted position. It is ensured that the monitoring equipment is as unaffected as possible to achieve the most precise neuromuscular data. Intravenous cannula will be placed in opposite hand than neuromuscular monitoring equipment.

Surgery:

Surgery with use of rocuronium 0.6 mg/kg for intubation.

Respiratory:

Patients are oxygenated at FiO2=1.0 during preoxygenation and induction of anesthesia until the trachea is intubated. Anesthesia continues initially with FiO2=0.30. Patients are ventilated with Pressure Control Ventilation, tidal volume 7 ml/kg, PEEP (positive end-expiratory pressure) 5 cm H2O and respiration frequency 10-12 targeting normocapnia (ETCO2 at 4.5-5.5 kPa). If PaCO2> 6 kPa primarily the respiration frequency (RF) will be increased. If hypoxemia arises, defined as SpO2< 95 or PaO2< 10 kPa primarily FiO2 will be increased. In the event of deficient effect, PEEP will be increased.

Fluid therapy:

1000 ml Ringer lactate is given intraoperatively. Blood loss up to 500 ml is replaced with Ringer lactate 1:2.5. Blood loss in excess of this is replaced in accordance with the local guidelines.

In case of hypotension ephedrine or phenylephrine will be administered. In case of need for continuous inotropic infusion phenylephrine or noradrenalin will be used.

Antibiotics:

According to local guidelines. Dose and name will be noted on the CRF.

Pain treatment:

Postoperative pain treatment with paracetamol, fentanyl, morphine and peripheral nerve blocks according to local guidelines.

PONV treatment:

PONV prophylaxis and treatment with ondansetron, dexamethasone and droperidol according to local guidelines.

Data collection

Perioperative data collection that will be noted in CRF:

Type of operation with operation code

TOF values (NMB sheet)

Body temperature measured immediately after intubation and again immediately before extubation

Intubating difficulty score

Operating time (from incision to last suture)

Statistics:

Normal distributed variables will be expressed by means and standard deviations; variables that are not normal distributed will be expressed by medians and interquartile ranges. Student´s t-test is used to compare normal distributed data and Mann-Whitney test to compare not normal distributed data.

X2-test or Fisher´s exact test will be used for frequencies when comparing the two groups.

Sample size:

We estimated a 20 seconds standard deviation for onset time of rocuronium based on previous studies[12]. We considered a difference in onset time of 30 seconds between the younger and elderly groups to be clinically relevant. We have calculated that a sample size of 16 patients in each group will allow us to detect this difference, with 5% Type 1 error risk and 90% power.

Schedule:

Inclusion of 2-3 patients per week is expected corresponding to duration of inclusion of approximately 10-16 weeks. Inclusion: Planned to go on in the period from December 2018 to April 2019. Inclusion of patients will be stopped when the desired number of patients is achieved. The trial will be counted as concluded, when the last patient has registered with the primary endpoint.

Data analysis and reporting: from April 2019 to June 2019.

Risks and side effects

Rocuronium: According to the product summary side effects are:

Not common (0,1-1%): Hypotension, anafylactic reaction.

Seldom (< 0,01%): Shock, angioedema, face edema.

Tracheal intubation with use of rocuronium is routinely performed at Department of Anaesthesia, Centre of Head and Orthopedics, 4031 Rigshospitalet. In both groups the patients will receive rocuronium in a dose aiming to provide optimal intubating conditions. It is not regarded as a disadvantage to use rocuronium, since the effect is monitored through surgery and if needed fully reversed by a reversal agent upon end of surgery.

Ethical considerations:

Tracheal intubation is as a standard performed with use of a rocuronium 0.6 mg/kg. Anesthesia and surgery will follow standard guidelines. The possible benefit in this trial is to investigate whether rocuronium 0.6 mg/kg has a different onset time in the elderly compared to younger patients. This may result in different intubating difficulty scores between younger and elderly patients. The results may help to detect the optimal dose of rocuronium for intubation of the trachea in elderly patients.

Consent and patient recruitment:

Patients are recruited among those referred to the Department of Anaesthesia, Centre of Head and Orthopedics, 4031 Rigshospitalet who meet inclusion criteria and who have no exclusion criteria.

The principal investigator is responsible for patient information and declaration of consent. In case the principal investigator is not able to interview the patient another investigator with GCP experience and medical knowledge within anaesthesia can perform the interview instead by referring to the principal investigator or sponsor. Written and oral patient information will be disclosed at the day of operation or 1-14 days before operation, during the preoperative anesthetic interview. This will be done in an undisturbed room. The patient will be offered the possibility of being accompanied by a family member or another person at the information interview. The patient will be informed that he/she will receive usual treatment if he/she does not want to participate, and that participation is voluntary, and that he/she always has the right to disclaim consent without affecting the further treatment.

After a period of consideration, depending on the patient´s needs and maximum 30 minutes before operation, an attempt will be made to obtain consent.

Informed consent will be obtained before the patients arrive to the operation ward. We thereby wish to avoid putting the patients in a situation where they in a stress-full environment at the operation ward have to decide about participation in the trial.

The trial will be reported to the Scientific Ethics Committees, Danish Medicines Agency and Danish Data Protection Agency. 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 "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt (Rights of Trial Subjects)" published by the Scientific Ethics Committee will be provided. 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. 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.

Quality control:

General procedures for quality control and quality assurance will be followed according to Good Clinical Practice guidelines.

Access to patients´ journals

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.

Data collection and storage:

Primary investigator will arrange for data collection and storage of CRFs 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 is covered by the obligation of confidentiality. The information about the patients is protected by the Act on processing of personal information and the Danish Health Act.

Responsible department:

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Publication:

The results, either 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). The right to data and know-how that emerges in connection with the trial will belong to the trial coordinator and the Department of Anaesthesia, Centre of Head and Orthopedics, 4031 Rigshospitalet, University of Copenhagen, Denmark.

Registration:

The study will be registered at www.clinicaltrials.gov

Economy:

Principal investigator and sponsor have taken the initiative to this trial.

Expenses in the trial are covered by departmental sources and covers salary for study investigators.

Patients participating in the trial will not receive financial compensation.

Patients participating in this trial are covered by the insurance “Patienterstatningsordningen” and “Ordningen om erstatning for lægemiddelskader”.

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