

RESEARCH PROTOCOL:

Reversal of vecuronium induced residual neuromuscular block with low doses of sugammadex: a randomized controlled trial.

This protocol has been translated from the Hungarian text submitted to the Ethics Committee.

Study team:

Béla Fülesdi: principal investigator and corresponding author,

László Asztalos: main investigator (patient selection, intraoperative measurements)

Zoltán Szabó-Maák: co-investigator (patient selection, intraoperative care)

Adrienn Pongrácz: designated for study drug, preparation and injection

Réka Nemes: designated to perform postoperative acceleromyographic measurements

András Gajdos: designated anesthesiologist for postoperative examinations

Szabolcs Lengyel: statistical advisor

Edömér Tassonyi: senior investigator and scientific advisor.

INTRODUCTION:

Severity of postoperative complications caused by residual neuromuscular block has shown the huge importance of fast and complete reversal of neuromuscular block at the end of the anesthesia. There are several disadvantages of using anticholinesterases as antagonists, Cardiac, pulmonary, neurologic and gastrointestinal side effects can appear due to cholinergic medication. Moreover, their usage is limited by their inability to antagonize deep neuromuscular block. The first curare antagonist with relaxant-binding property named sugammadex (Bridion) brought a breakthrough in the solution of these two problems. This drug has proven to be particularly effective in reversal of total, deep and moderate block induced by the aminosteroid relaxant rocuronium (Esmeron®), (train of four count TOFC:0, post tetanic count PTC: 0). The

effective doses of sugammadex in these cases are 16 mg/kg, 4 mg/kg and 2mg/kg depending on the depth of the blockade. According to the results of a recent study conducted in our department, the dose of sugammadex 1 mg/kg is sufficient to antagonize a residual neuromuscular block at the reappearance of all four twitches in response to train-of-four (TOF) stimulation: threshold: TOF count of four (TOFC 4) rocuronium induced block..

Sugammadex was proved to be suitable for antagonizing other steroidal type muscle relaxants such as vecuronium (Norcuron®) and pipecuronium.. The recommended doses of sugammadex to antagonize vecuronium induced block are identical to ones used for the reversal of rocuroniumat moderate and deep block.

The residual block (TOFC 4) has lower intensity than the moderate block (TOFC 2), but as the adequate doses of sugammadex to eliminate the residual muscle paralysis of vecuronium has not been determined so far, Therefore, administration of 2mg/kg sugammadex - the dose used in moderate block – is also recommended for the reversal of TOFC 4 block. According to our experience, at the end of anesthesia the most often a residual block is present, which is reversed in current practice by neostigmine, However, sugammadex is faster, more reliable and has no major side effects compared to neostigmine and therefore from a clinical perspective it may have significant advantages versus neostigmine to reverse a TOFC 4 block. As the cost of sugammadex is relatively high its routine use is limited. The administration of a 2 mg/kg dose to an average adult patient costs nearly 100 EUR (30 000 HUF), which is too much for the public health system.

Our hypothesis is, that lower doses than sugammadex 2 mg/kg should be enough to reverse residual vecuronium block, allowing to reduce the costs of the treatment and facilitating the wider use of the drug. The primary aim of this study is to determine the lowest sugammadex dose which can effectively and permanently antagonize the residual vecuronium block. The secondary aim is to study whether postoperative recurarization occurs after low sugammadex doses.

METHODS

Five parallel-arm, randomized, placebo controlled, superiority trial

Patients undergoing elective surgery that requires intubation of the trachea but not maintenance of full relaxation during the whole operation will be asked to participate. The research team will select patients for the study..

Eligibility criteria for participants

- 65 adult surgical patients, who have signed the informed consent to participate in the study will be enrolled
- age:18-65 years
- American Society of Anesthesiologists physical status 1-3
- BMI: 18,5-25 (normal body weight)
- male/female equal in number
- length of surgical procedures should be at least 50 minutes
- surgical procedure requiring intratracheal intubation
- patient position is supine with one arm freely accessible

Exclusion criteria

- Diseases influencing neuromuscular function (myopathies, severe liver and kidney failure)
- drugs influencing the neuromuscular function (magnesium, aminoglycosides)
- expected difficult airway
- pregnancy (pregnancy test was performed for every fertile female participants)
- lactation
- acute surgery
- COPD
- bronchial asthma

- glaucoma

Location of the trial:

Department of Anesthesiology and Intensive Therapy, University of Debrecen, Medical and Health Science Center, Debrecen, Hungary.

Preparation, monitoring, anesthesia

After arriving in the OR insertion of peripheral venous line, Ringer- lactate solution is infused continuously. One freely accessible arm has to be provided solely for the purpose of neuromuscular monitoring, avoiding the placement of NIBP cuff on this side. Vital signs and temperature monitoring end tidal carbon-dioxide, sevoflurane and oxygen monitoring.

Balanced anesthesia protocol routinely used in our department

- premedication with 7,5mg midazolam orally
- pre-oxygenation
- induction of anesthesia with 2µg/kg fentanyl and 1,5-2-5mg/kg propofol and 0,1 mg/kg vecuronium (Norcuron®)
- ventilation after intubation with sevoflurane (age-corrected MAC 1-1,5)
- and air/oxygen mixture in IPPV mode
- maintenance of anesthesia with sevoflurane (with continuous monitoring of end tidal concentration)
- fentanyl boli on clinical need
- repeated administration of 0,01mg/bwkg vecuronium when reaching TOFC1
- variation limit of arterial blood pressure 15%
- end tidal carbon dioxide: 38-40 mmHg
- core temperature $T > 36^{\circ}$
- skin temperature over the monitored muscle $T > 32^{\circ}$
- SpO₂ 98-100%

Neuromuscular function measurements

The monitoring consists of recording the musculus adductor pollicis responses evoked by supramaximal stimulation of the ulnar nerve on the wrist. To do this, we use the TOF-WATCH SX acceleromyograph. The free arm is fixed on an arm board and a hand adapter is placed on the palm ensuring a preload to the thumb. A piezoelectric crystal is attached to the thumb which senses the movements of the thumb. The other fingers are carefully immobilized in order to prevent artifacts. After cleansing the surface, two transcutaneous electrodes are positioned above the ulnar nerve. After induction of anesthesia TOF stimulation is delivered automatically every 15 seconds for 2-3 minutes. This is followed by a 5 s 50 Hz tetanisation, then a two minutes pause followed by a C2 type automatic calibration of the acceleromyograph to determine the supramaximal stimulus intensity. Finally the TOF stimulation runs for two minutes, and if the signal is stabilize the relaxant is administered. The device delivers automatically the trains of TOF stimuli/15 sec. After cessation of muscle responses the trachea is intubated. The stimulation runs throughout the whole examination the signals are recorded on a computer for later analysis. The evaluation is based on the TOF response (in other words the ratio of the forth to the first evoked response T_4/T_1). Without relaxant, there are four equal responses for a TOF stimulation, this is a 100% TOF (a TOF ratio 1.0) control value. This ratio decreases due to relaxant effect, until the response disappears (the TOF ratio is zero). The recovery from the block is quantified by the TOFC that is the number of responses that reappears to stimulation. These are referred as TOF count (TOFC 1,2,3,4). Once the 4 TOF returned, the TOF ratio is determined. The device automatically calculates it. The return of the 4th twitch to TOF stimulation is defined as threshold TOFC-4 block, or residual block. The block is fully reversed when the TOF ratio reaches 100% (first picture). This value is compared to the values measured before administering the relaxant (normalization), and this normalized TOF ratio is determined later (offline) from the recorded data. Furthermore, the amplitude of the response (strength of the muscle contraction) is determined which is referred as T1 because it is the first of the four twitches to TOF stimulation (T1%).

The following variables will be evaluated:

1. TOF count (TOFC-4): the number of evoked responses to TOF stimulation
2. TOF ratio the relation of T4/T1
3. Normalized TOF ratio: measured TOF ratio/control TOF ratio (before administration of the relaxant)
4. First response (T1): the strength of the response given for the first TOF stimulus (control %)
5. Elapsed time from administration of the antagonist to TOF 0,9
6. Elapsed time from administration of the antagonist to non-normalized TOF 100%
7. Elapsed time from administration of the antagonist to T1>90

Measuring the reversal of the neuromuscular block

Patients will be randomly assigned for one of the five treatment group to receive sugammadex 0,5; 1,0; 2,0 mg/kg or neostigmine 0,05 mg/kg with atropine 0,015 mg/kg or placebo (saline)

The residual block (threshold TOFC-4) is reversed at the end of surgery - when all of the four responses reappeared after three consecutive TOF stimulations. The TOF ratio at this moment will be determined. The reversal agent is prepared by a designated anesthesiologist (PA) according to a randomization code and injected on the request of the investigators (LA and ZSM) who are blinded to the drug. The anesthesiologist who prepares the drug is not allowed to take

part in the online measurement of the effect of the study drugs. The syringes contain the different drugs as identical amounts of transparent liquid.

Method of randomization

The statistical advisor (SL) will provide the randomization list using a computer program (www.randomizer.org). The nature of randomization is 1:1 to ensure equal number of cases in the treatment groups. The patients, the investigators and the anesthesiologists who measure the postoperative TOF ratios will be blinded to the drugs injected. The effect of reversal is recorded on the computer equipped with a special program (TOF-Watch-SX software version 2.2 INT).

Outcome measures.

The primary end point is the time elapsed between the start of administration of the reversal agent and achievement of 100% TOF ratio. This can be measured online. If this state is not reached in 30 minutes, the patient receives 2 mg/kg sugammadex before the extubation to reverse the residual block. This is accurately documented and considered as failed reversal. The patient can only be extubated, when amongst other criteria, the TOF ratio returns to 100%.

Derived parameters such as normalized TOF 0,9 will be calculated offsite from the recorded data. The secondary end point is the incidence of postoperative recurarization after sugammadex vs. neostigmine reversal.

After extubation, the patients are transported to the recovery room, where the designated anesthesiologists (RN, AG) will continue the neuromuscular measurements and the monitoring of vital signs. Three consecutive TOF stimulations will be delivered at 0, 20, 40, 60 minutes which will be recorded for later analysis. Clinical signs of recurarization will be sought for, such as head lift test, muscle weakness, difficulty swallowing, respiratory depression, oxygen desaturation or double vision. After 60 min in the recovery room, patients will be transferred to the ward and observed for 24 hours to explore eventual side effects.

The trial ends following the 24-hour-long observation of the last patient.

Statistics

Calculation of sample size was carried out assuming that the usual time for recovery is 600 s with an SD of 200 s in patients treated with neostigmine and that sugammadex 0.5 mg/kg decreases the time of recovery to 300 s. Using a Type I error rate (α) of 0.05 n of 10 in the treatment groups would be needed to reach a power of 0.8. As we assumed that dropouts might occur, we included 13 patients in each group, bringing the total to 65 patients.

Data are registered via computer by the anesthesiologists responsible for the study. The elapsed time required to reverse the block will be compared between the groups with the use of appropriate statistical tests. The number of patients whose TOF ratio did not reach 100% and T1 did not reach 90% will be recorded.

Ethical considerations

Patients receive written information (not presented here), and their signed consent is required to include them in the study and to use their health data. They agree voluntarily to participate in the study and to provide their health data for research use knowing that they can withdraw it any time later without suffering any negative consequences. Vecuronium, sugammadex, neostigmine and atropine are all registered drugs in Hungary. The examinations do not include any invasive or possibly harmful intervention. Neuromuscular monitoring is routine clinical practice during anesthesia. Patients are informed about the nature of neuromuscular monitoring, the possible pain due to nerve stimulation, and the possibility to refuse it at any moment.

The examinations do not have extra time cost in the operation room, do not lengthen the anesthesia, on the contrary, time spare is expected.

The only extra cost of the study is the purchase of sugammadex.

Note: CONSORT 2010 recommendations were considered when elaborating the research plan

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