Effect of reversal of neuromuscular blockade on the amplitude of motor evoked potentials: A randomised controlled cross-over study comparing sugammadex and placebo

Protocol Version: 1.0

Protocol Date: 20 April 2018

ClinicalTrials.gov ID: NCT03087513

Effect of reversal of neuromuscular blockade on the amplitude of motor evoked potentials: A randomised controlled cross-over study comparing sugammadex and placebo

Investigators

1. Nathan Royan MBBS FANZCA. Department of Anaesthesia, Toronto Western Hospital, University of Toronto

2. Lashmi Venkatraghavan MD, FRCPC. Department of Anaesthesia, Toronto Western Hospital, University of Toronto

3. Atul Prabhu FRCA, FRCPC. Department of Anaesthesia, Toronto Western Hospital, University of Toronto

4. Pirjo Manninen MD, FRCPC, Department of Anaesthesia MD, Toronto Western Hospital, University of Toronto

5. Gina Bastaldo MSc CNIM. Department of Surgery and Anaesthesia, Toronto Western Hospital, University of Toronto

6. Roger Sarjeant MSc CNIM, Department of Surgery and Anaesthesia, Toronto Western Hospital, University of Toronto

7. Eric Massicotte MD, MSc, FRCS (C), Division of Neurosurgery, Toronto Western Hospital, University of Toronto

1. Project Summary

Intraoperative monitoring of the motor evoked potentials has been shown to be both a sensitive and specific indicator for detecting intraoperative neurologic injuries during spine surgery.(Fehlings, Brodke et al. 2010) It is utilised whenever there is risk for injury of nerve roots or the spinal cord during the procedure.

Anaesthetic agents, especially the inhaled volatile anaesthetics and muscle relaxants, are confounders for motor evoked potential monitoring as they have deleterious effects on the amplitude of motor evoked potentials.(Sekimoto, Nishikawa et al. 2006) Hence, total intravenous anaesthesia with no intraoperative muscle relaxants, are the standard anaesthetic technique for these surgeries.

Muscle relaxants are usually required during the induction of anaesthesia and endotracheal intubation of larynx. Current practice is to wait for the resolution of residual neuromuscular blockade before the motor evoked potential recordings (MEPs) are initiated and this makes it difficult to assess if there was any neurological injury associated with positioning of the patient. A previous case series has

shown that reversal of muscle relaxant can improve the amplitude of MEPs.(Batistaki, Papadopoulos et al. 2012)

The aim of this study is to perform a randomised controlled trial to study the changes in motor evoked potential amplitudes comparing sugammadex and placebo.

2. Background

Intraoperative monitoring (IONM) is most frequently employed in patients where the spinal cord or nerves are considered at risk. This may be evident through patient symptoms, pathological process or appearance on imaging.

Trained neurophysiologists that work in concert with the surgeon and anaesthesiologist perform the intraoperative monitoring. The monitoring commences once the patient has received general anaesthesia. Small electrodes are placed under the skin of the scalp and peripheries and different electrical stimuli are delivered to evoke a measured response. The neurophysiologist is able to monitor different potentials (motor evoked potentials, somatosensory evoked potentials, electromyography) and assess for a significant change.

Motor evoked potential monitoring is a well-established and safe intervention to assist in prevention of intraoperative injury during spine surgery.(Schwartz, Sestokas et al. 2011) There is no current consensus for criteria for change in amplitude for trans-cranial motor evoked potential monitoring. The peak-peak amplitude of the baseline motor evoked potential is utilised as a monitoring tool during surgery. The smaller the change in amplitude that is utilised as alarm criterion the more false positives that will be conveyed to the surgeons. (Legatt, Emerson 2016) Our neurophysiologists use a decrease in the amplitude by more than 50% or loss of the signal as a trigger to warn the surgeon of potential development of a neurological insult or injury.

The usual anaesthetic practice at our institution for patients undergoing posterior cervical spine surgery is to administer muscle relaxation to aid intubation at the start of the case and occasionally small doses of rocuronium (10-20mg) prior to turning the patient prone. The neuromuscular blockade is then allowed to wear off and the neurophysiologist will attempt to record their baseline motor evoked potentials during or just prior to surgical exposure.

A peripheral nerve monitor may be used to monitor the degree of residual neuromuscular blockade. This is standard anaesthetic equipment with the most common mode to assess residual blockade used being a train of four count. This involves adhesive dots applied over the ulna nerve and a current applied (approximately 70-80mA) in a train of four impulses 0.5 seconds apart with a pulse width of 250 microseconds. It is a safe method of assessing the occupancy of

acetylcholine receptors at the neuromuscular junction by observing the number of twitches displayed in the peripheral muscle (e.g thumb movement).

Number of twitches

0- 100% receptors blocked
1- 90% receptors blocked
2- 75-80% receptors blocked
3- 75% receptors blocked
4- 0% receptors blocked

For the purposes of our study we plan to continuously monitor the train of four count and ratio using a peripheral nerve stimulator module that is built into the anesthesia machine (GE Datex Ohmeda). The train of four count on both measuring tools will be delivered as a train of four impulses 0.5 seconds apart (2Hz) at 70-80mA with a pulse width of 250 microseconds.

Our current approach does not involve routine measurement of the degree of residual neuromuscular blockade with a peripheral nerve stimulator. This is a safe approach as monitoring is achievable with partial blockade but may not necessarily be most beneficial in patients with existing neurological impairment as complete reversal of neuromuscular blockade is not ensured.(Li, Song et al. 2010)

The issues with this current technique are;

a) Patients cannot be monitored for neurological changes during their transfer into the prone position
b) There is likely residual neuromuscular blockade decreasing the amplitude of motor evoked potentials

A cases series of 10 patients in healthy subjects undergoing lumbar spine surgery demonstrated a 74% increase in mean amplitude of the MEPs with reversal of neuromuscular blockade with sugammadex 2mg/kg.(Batistaki, Papadopoulos et al. 2012)

We plan to perform a randomised controlled cross over trial comparing the change in MEP amplitudes with administration of sugammadex or placebo. This will be performed on at risk patients (e.g. cervical myelopathy) undergoing posterior cervical spine surgery where MEPs can be more difficult to attain but of higher utility.(Kombos, Kopetsch et al. 2003)

The crossover arm of the trial is to enable patients to function as their own control group. During surgical closure patient will remain on a total intravenous anaesthesia (propofol and remifentanil). When the patient returns to a train of four count of 2 or more on peripheral nerve monitor repeat motor evoked potentials will then be recorded and

patients will receive the alternate drug to the one received in the initial arm of the trial.

The purpose of this study is to determine the increase in amplitude of the motor evoked potentials when residual neuromuscular blockade is reversed with sugammadex or placebo.

4. Hypothesis

We hypothesize that reversal of neuromuscular blockade by sugammadex will increase the amplitude of motor evoked potentials compared with placebo.

5. Significance of the study

Facilitating increased amplitudes of MEPS via reversal of residual neuromuscular blockade will enable increased accuracy of monitoring.

Providing the option of reversal of neuromuscular blockade will allow MEPs to be monitored during patient positioning to prevent placing them in a neurologically compromising position.

6. Methods

6.1 Research Design

This is a prospective, single centre, triple blinded randomised controlled cross-over trial. Patients who are scheduled for an elective posterior cervical spine procedure in prone position and require motor evoked potential monitoring (MEPs) will be included. Patients will be randomised to assign to one of the following treatment sequences: sugammadex followed by placebo, or vice versa. The primary outcome is the change of MEP amplitude of the first dorsal interossei from baseline 3 minutes after administration of the allocated intervention. The patients, anesthesiologists and neurophysiologists (outcome assessor) will be blinded for the allocated intervention group.

The first study intervention will be performed after the patients are positioned in prone with a train of four count of 2 and satisfactory baseline motor evoked potentials have been recorded. This will likely occur during or just prior to surgical exposure.

The second study intervention will be performed during surgical closure. This will be once the surgeons have completed their use of motor evoked potentials and the patient remains on total intravenous anaesthesia (propofol and remifentanil). A minimum washout period of 100 min after the last bolus dose of rocuronium (equivalent to 5 half lives) is required and the completeness of washout will be confirmed with no residual tetanus fade, fade on train of four (or fading in double burst stimulation) on a peripheral nerve stimulator. The operative time

of posterior cervical spine procedure is usually around 3 hours and should allow complete washout of rocuronium. After the preconditions are achieved on peripheral nerve stimulator or the direct train of four monitor, the second intervention (either sugammadex or placebo) will be administered.

On each occasion the increase in amplitude of the motor evoked potential of both upper and lower limbs will be assessed at 3,6,9,12 and 15 minutes post intervention.

6.2 Trial Population

The study participants will be recruited from patients admitted to Toronto Western Hospital for elective posterior cervical spine surgery requiring motor evoked potential monitoring as per the admitting surgeon.

Inclusion criteria

- All adult patients aged 18-80 years with ASA class I-III undergoing cervical spine surgery in the prone position with motor evoked potential monitoring.
- Operation time greater than 3 hours

Exclusion criteria

- Allergy to propofol or documented egg allergy
- Known allergy to sugammadex
- Severe renal dysfunction (EGFR<30)
- British Research Medical Council (BRMC) motor grading <3 in any peripheral muscle group pre-operatively. This is inability to move the muscle group against gravity.
- Surgical requirement of strict muscle relaxation for surgical exposure
- Lack of informed consent
- Pregnancy
- Loss of MEPs signals during washout period (or intraoperative spinal cord injury resulting in irreversible loss of MEP)

6.3 Recruitment

All patients who are admitted to Toronto Western Hospital and satisfy the above criteria will be considered for enrolment into the study. Informed consent will be sought as detailed in section 12. A record will be kept of all eligible patients who are not enrolled and reasons for non-enrolment.

6.4 Randomisation Method

Enrolled patients will be randomised according to a computer based, permuted block randomisation method, with a 1:1 allocation ratio and a variable block size of 4-6.

6.5 Allocation Concealment

Sequentially numbered, opaque, sealed envelopes will be used for allocation schedules and individual assignments. The study envelope will be opened at the beginning of each case by a trained research assistant and the reversal drugs will be prepared.

6.6 Blinding

This is a randomised blinded study where the administering anaesthetist, surgeon and neurophysiologists will be blinded to the intervention. The study patients will receive a 10ml syringe containing either sugammadex or placebo (saline 0.9%) to be administered in a 1mls per 10kg basis (up to 100kg).
Further, a blinded research assistant will perform assessment, data collection, and analysis of neurophysiology data attained.

7. Protocol

7.1 Standard Perioperative Care

Routine standard preparation of the patients will be carried out as per our institutional standard for patients undergoing spine surgery. All routine physiological monitoring (e.g. ECG, invasive arterial blood pressure, Sp02, end tidal C02, temperature and depth of anaesthesia monitoring) will be performed.

The induction of anaesthesia will be performed with propofol (2-5 mg/kg), fentanyl (2-3mcg/kg) and rocuronium (0.6mg/kg) following calibration of the peripheral nerve stimulator. The patient's trachea will be intubated once the peripheral nerve stimulator shows no twitches. The time of induction and rocuronium dose must be strictly recorded. After tracheal intubation the lungs will be ventilated to maintain a PaC02 between 33-35mmHg. Maintenance of anaesthesia will be with desflurane inhalational anaesthesia titrated to entropy 40-60 until final operative position is achieved.

Hemodynamic management will target a mean arterial pressure (MAP) >70 mmHg using standard inotropes and/or vasopressors (e.g. phenylephrine and ephedrine)

Prophylactic antibiotics and dexamethasone will be administered as per surgical request and institutional practice. Analgesia should be administered with fentanyl in additional 25mcg boluses up to the completion of surgical exposure and then left to clinical judgement

there-onwards. Anti-emetics should be administered as per the anaesthesiologist practice.

Patients should undergo peripheral nerve monitoring following the induction via a peripheral nerve stimulator and by a direct train of four monitor by the neurophysiologists.

On completion of the cross over arm of the trial, the patient may be changed to volatile anaesthesia as per institutional practice and extubated based on anaesthesiologist clinical judgement. Use of a nerve stimulator to assess the train of four count with reversal of residual neuromuscular blockade with neostigmine and glycopyrrolate if deemed appropriate at the end of the case is recommended.

Post-operative anaesthetic care will occur in the recovery room as per standard practice in terms of oxygen therapy, monitoring and assessment of neurological status, pain, nausea, vomiting and degree of sedation. Fentanyl 25mcg iv will be administered every 5 mins up to a maximum of 200mcg to maintain a Numeric Pain Score <4 of 10. Morphine or Hydromorphone will be used for additional analgesia after fentanyl. Nausea may be managed with dimenhydrinate 25-50mg IV and ondansetron 4m IV.

7.2 Study Protocol

Patients should undergo peripheral nerve monitoring following the induction via a peripheral nerve stimulator and by a direct train of four monitor by the neurophysiologists. The train of four should be assessed on peripheral nerve stimulator and on the neurophysiology monitoring prior to turning the patient prone. If the patient has two or more twitches on either monitoring they should be given 0.1mg/kg rocuronium prior to positioning prone.

Once the patient is in their final position for surgery the anaesthetic will be changed to a total intravenous anaesthetic (TIVA) with propofol and remifentanil titrated to entropy of 40-60. The volatile anaesthesia has to be washed out with high flows of 10L/min until end tidal desflurane is less than or equal to 0.2.

When the above conditions are met the train of four count (TOFC) will be checked by the anaesthesiologist. When the TOFC is 2 or more the baseline motor evoked potentials (bMEPs) will be performed.

Following the bMEPs the anaesthesiologist will administer the reversal drug (either sugammadex 2mg/kg in 10 ml syringe or matching placebo). This time must be strictly recorded, as it is the time that has elapsed since the induction dose of muscle relaxant. The neurophysiologist will perform and record MEPS at 3,6 and 9 minutes post reversal dose. The following parameters will continuously be monitored during the study period: TOFC, Entropy, BP, HR, CO_2,

peak airway pressures, anaesthetic infusion rates, temperature and oxygen saturation. If the testing occurs during surgical exposure it is important to ask the surgeons to make a very brief pause to allow the motor testing to be performed and to check the entropy at the same time.

Following surgery commencement there will be a surgical grading of the relaxation of the surgical field once exposure attained and collection of surgeon stated observation of patient movement.

The operative time of posterior cervical spine procedure is usually around 3 hours and should allow for complete washout of rocuronium. A minimum washout period of 100 min after the last bolus dose of rocuronium (equivalent to 5 half-lives) is required and the completeness of washout will be confirmed with no residual tetanus fade, no fade on train of four (or fading in double burst stimulation) on a peripheral nerve stimulator.

The crossover arm of the trial will occur during surgical closure at the end of the operation when the surgeons have finalised their use of the monitoring and the patients are still receiving total intravenous anaesthesia (propofol and remifentanil). If needed, each patient will be given 0.1mg /kg rocuronium to facilitate surgical closure. When the train of four count is of 2 or more the patients will be administered the cross-over drug (placebo if received sugammadex initially and vice versa) and the motor evoked potentials and same anaesthetic variables as above will be recorded for 3,6 and 9 minutes post cross-over dose.

8. Assessment

8.1 Baseline Measurements

At the time of enrollment, the following data will be collected for all participants: patient demographics, preoperative neurological function, comorbidities, allergies, baseline physiological variables (blood pressure, heart rate, O2 saturations, weight) and procedure details.

8.2 Outcome Measurements

Primary Outcome Measure

The primary outcome measure is the increase in amplitude of the motor evoked potential measurements of the first dorsal interosseus muscle at 3 minutes following reversal of residual muscle relaxation with either sugammadex or placebo.

Secondary Outcome Measures

- Changes in the amplitude of the MEPs from the baseline in the first dorsal interosseous muscle at 6 and 9 minutes

- Side effects of reversal (hemodynamic changes, respiratory changes, surgeon observed patient movement, requirement for additional muscle relaxation and the anesthetic agents]
- Grading of relaxation of the surgical field by the surgeons using a four-point Likert scale (poor, acceptable, good and optimal) .

9. Data Collection and Management

9.1 Data Collection

The following data will be collected (see attached Data Collection Form):

Administrative Data

Screening log- detailing numbers of potential participants screened for inclusion and reasons for exclusion and numbers actually recruited.

Demographic data

Age, sex, height, weight, American Society of Anaesthesiologists physical class (ASA)

Study Data

Baseline data as detailed in section 8
Outcome data as defined in section 8

9.2 Data Management

An electronic data management system will be used. All data will be entered directly on the electronic system. Data will be acquired on a Research laptop and also the Monitoring Laptop of the neurophysiologist. Following the case, data will be transferred from the Neurophysiologist laptop to the Research database where it will later be analysed.
Pre specified automated data entry checks will be performed on all entered data to prevent the entry of impossible values or the omission of key data fields. All study databases will be in the password protected UHN server. Any data containing participant identifying details will be stored separately and securely from study documents.

10. Sample Size

10.1 Hypotheses

Null Hypothesis- There is no difference between the amplitude of the baseline motor evoked potentials before and after reversal with sugammadex or placebo.

Alternative Hypothesis- There is a difference in the amplitude of the baseline motor evoked potentials before and after reversal with sugammadex or placebo.

10.2 Sample size

A previous observational study reported sugammadex increased the amplitude of MEP by 74% (Batistaki, Papadopoulos et al. 2012). The normal upper limb MEP amplitude (first dorsal interosseus) is 2000 +/- 1600 microV from a previous published cross-over study in MEP (Chong, Manninen et al. 2014). Based on the assumption that the within-patient standard deviation of the MEP amplitude is 1600 microV and a power of 80%, a total of 30 patients is required in this two-intervention crossover study for detecting a treatment difference of 1200 microV (60% increment) at a two-sided 0.05 significance level. The sample size will be increased to 40 patients (20 patients per group) to cater for a potential 15-25% drop-out rate during the study.

11. Analysis

Statistical analysis will be performed using SPSS statistical software (version 14). The data distributions will be tested for normality with the Kolmogorov–Smirnov test. Descriptive statistics will be summarised as mean (± SD), median [Interquartile range (IQR)] or number (%) as indicated. The Mann-Whitney U test will be performed to compare the amplitude values of the two groups. TOF count, grades of surgical relaxation will be compared using the Chi-square test or Fisher's exact test according to the expected counts. In all cases, a P-value of 0.05 will be considered statistically significant.

12. Ethical aspects

12.1 Regulatory approval

Regulatory approval will be sought from the local research ethics board and the study will not commence until it is obtained.

12.2 Informed consent

Prior to enrolment potential participants will receive written and verbal information regarding the nature and purpose of the study, what participation involves and potentials benefits and risks. They will be given time to ask questions and it will be emphasised that participation is voluntary, that they are free to withdraw from the study at any time and that any decision to do so will not affect any treatment they would otherwise receive. Where the participant understands and accepts these terms, they will be asked to sign the consent form.

12.3 Privacy and Confidentiality

The laptop and all data transferred to the research database used in the study will contain only de-identified data and it will be encrypted as per UHN policy 1.40.006 Storage, Transport and Destruction of Confidential Information.

References

Batistaki, C., et al. (2012). Sugammadex to reverse rocuronium and facilitate intraoperative motor evoked potentials monitoring during spinal surgery. Anaesth Intensive Care 40(6): 1073-1074.

Chong, C. T., et al. (2014). Direct Comparison of the Effect of Desflurane and Sevoflurane on Intraoperative Motor-evoked Potentials Monitoring. Journal of Neurosurgical Anesthesiology 26(4): 306-312.

Fehlings, M. G., et al. (2010). The evidence for intraoperative neurophysiological monitoring in spine surgery: does it make a difference? Spine (Phila Pa 1976) 35(9 Suppl): S37-46.

Kombos, T., et al. (2003). Does preoperative paresis influence intraoperative monitoring of the motor cortex? J Clin Neurophysiol 20(2): 129-134.

Li, C. X., et al. (2010). Effect of the degree of muscle relaxation on motor-evoked potential elicited by transcranial electrical stimulation in spine surgery. Nan Fang Yi Ke Da Xue Xue Bao 30(12): 2686-2688.

Plummer-Roberts, A. L., et al. (2016). Residual Neuromuscular Blockade. Aana j 84(1): 57-65.

Schwartz, D. M., et al. (2011). Transcranial electric motor evoked potential monitoring during spine surgery: is it safe? Spine (Phila Pa 1976) 36(13): 1046-1049.

Sekimoto, K., et al. (2006). The effects of volatile anesthetics on intraoperative monitoring of myogenic motor-evoked potentials to transcranial electrical stimulation and on partial neuromuscular blockade during propofol/fentanyl/nitrous oxide anesthesia in humans. Journal of Neurosurgical Anesthesiology 18(2): 106-111.

Alan D. Legatt, Ronald G. Emerson, Charles M. Epstein, David B. MacDonald, Vedran Deletis, k Ricardo J. Bravo, and Jaime R. López A (2016). CNS Guideline: Transcranial Electrical Stimulation Motor Evoked Potential Monitoring J Clin Neurophysiol 33: 42–50.