Effect of intraoperative muscle relaxation reversal on the success rate of motor-evoked potential recording in patients undergoing spinal surgery: study protocol for a randomised controlled trial

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ABSTRACT

Introduction Transcranial motor-evoked potentials (TcMEPs) is conventionally performed without neuromuscular blockade (NMB) because of its potential interference with neuromuscular junction and signal interpretation. Sugammadex is the first highly selective antagonist that binds to rocuronium and can rapidly and effectively reverse NMB. This study aims to evaluate the success rate of intraoperative muscle relax reversal by sugammadex on intraoperative TcMEP recording.

Methods and analysis We will conduct a single-centre randomised controlled study. In total, 162 patients undergoing thoracic or lumbar spinal surgery will be randomly divided into the sugammadex group or control group at a ratio of 1:1. Total intravenous anaesthesia by propofol and remifentanil will be performed in both groups. In the sugammadex group, patients will receive continuous infusion of sugammadex to produce a blockade maintained for at least two twitches in train-of-four, rocuronium infusion will be discontinued and 2 mg/kg sugammadex will be given while performing TcMEPs monitoring. In the control group, rocuronium infusion will be discontinued and the same volume of saline will be infused while performing TcMEPs monitoring. The primary aim of this study is to evaluate the success rate of TcMEPs recording between two groups.

Ethics and dissemination The approval for the study was certificated by the Ethical Committee of Beijing Tiantan Hospital, Capital Medical University on, 16 July 2021 (KY2021-082-02). The study was registered on clinica trials.gov on 25 October 2020. Our study might guide neuromuscular blockade plans in TcMEPs monitoring undergoing spinal surgery. The findings of the study will be published in peer-reviewed journals and will be presented at national or international conference.

Trial registration number NCT04608682.

BACKGROUND

Intraoperative neuromonitoring (IOM) uses a combination of motor-evoked potentials (MEPs) and somatosensory-evoked potentials (SSEPs) to assess neural integrity during spinal surgery. This method is dependable and validated for assessing spinal cord function. Current guidelines suggest that MEPs are superior to SSEPs as diagnostic adjuncts for functional and structural integrity monitoring of the motor system, particularly during high-risk surgery.1 Transcranial motor-evoked potentials monitoring (TcMEPs), which are muscle action potentials elicited by transcranial brain stimulation, have been the most popular method of IOM in recent decades. Electrical stimulation applied over the motor cortex activates the corticospinal/corticobulbar pathways, lower motor neurons and neuromuscular junctions, allowing compound motor action potentials to be recorded peripherally.2

Strengths and limitations of this study

This study is a randomised controlled trial to evaluate the success rate of intraoperative muscle relaxation reversal by sugammadex on intraoperative transcranial motor-evoked potentials recording under partial neuromuscular blockade (NMB) or no NMB.

This study has a strict randomised system, clear inclusion and exclusion criteria and a rigorous uniform protocol to manage haemodynamic and respiratory parameters and depth of anaesthesia in both groups.

The abductor pollicis brevis muscles are chosen to check the transcranial motor-evoked potentials monitoring recording results, this may limit the generalisation of our data to other muscle groups especially from lower limb muscles.
The TceMEP signals are exquisitely sensitive to inhaled anaesthetics and neuromuscular blockade (NMB), and studies have shown that inhaled anaesthetics could suppress TceMEPs in a dose-dependent manner, NMB acts at the neuromuscular junction and results in a dramatic loss of TceMEP signals. For most cases requiring TceMEPs, the use of NMB is avoided except during intubation performed with a rapid-acting agent. Our previous study established a practicable anaesthetic regimen for TceMEPs, which consists of total intravenous anaesthesia using propofol and remifentanil without the use of NMB.

However, appropriate muscle relaxation optimises anaesthetic management, facilitates surgery and prevents patient movement. For some surgical procedures, such as large deformity cases requiring extensive dissection, a muscle relaxant is desired by surgeons and total avoidance of NMB might increase the risk of bleeding. However, NMB comes at the expense of potential increased rates of false interpretation or undetectable responses of TceMEP signals. Thus, the ideal use of NMB for TceMEPs monitoring is still controversial. Partial NMB (pNMB) has been applied in TceMEPs monitoring for a long time. The recommended blockade for pNMB is $T_1$ between 5% and 50% baseline or one or two twitches measured by train-of-four (TOF). Kalkman maintained pNMB at $T_1$ twitch height of 5%–15%, whereas additional classification of pNMB aimed at $T_1$ twitch height of 45%–55% by van Dongen led to contrasting results. Liu et al have shown pNMB with TOF ration aimed at 26%–50% for TceMEPs or 16%–50% for TceMEPs seems to be an appropriate regimen for TceMEPs during surgical correction for idiopathic scoliosis under Total Intravenous Anesthesia (TIVA). Nevertheless, the incidence of monitoring failure and false-positive results was increased under pNMB.

Sugammadex is a modified γ-cyclodextrin derivative that selectively binds to NMB (rocuronium and vecuronium), which can encapsulate rocuronium and reverse the rocuronium-induced NMB at the neuromuscular junction. The efficacy of reversing various levels of rocuronium block has been confirmed by multiple studies. The advised sugammadex dose for reversal of a moderate NMB (at least one twitch in a TOF) is 2 mg/kg, and sugammadex at 4 mg/kg is advised for reversal of a deep NMB (no twitches in a TOF and at least one twitch in a post-tetanic count). With these doses, it takes 2–3 min on average to reverse NMB. However, concerns related to sugammadex-induced hypersensitivity reactions such as anaphylaxis and cardiac arrhythmias consistently exist. These adverse effects are occasionally life-threatening and require further studies.

To the best of our knowledge, no convincing evidence of prospective study exists that evaluates the use of sugammadex to reverse the effect of rocuronium during TceMEPs. Therefore, this study is a randomised controlled trial to compare the success rate of TceMEPs recording under pNMB and no NMB reversed by sugammadex. We hypothesise that the muscle relaxation reversal effect of sugammadex can increase the success rate of TceMEPs recording in spinal surgery.

**METHODS/DESIGN**

**Study design**

This study is a prospective, single-centre, parallel-group, assessor-blinded and randomised controlled trial. Patients will be screened and recruited consecutively in Beijing Tiantan Hospital, Capital Medical University. The trial has been approved by the Institutional Review Board of Beijing Tiantan Hospital (KY2021-082-02) and registered 25 October 2020.

**Study population**

Patients undergoing thoracic or lumbar spinal surgery with TceMEPs monitoring will be screened for eligibility. The inclusion criteria will be as follows: age range from 18 to 65 years old, and American Society of Anaesthesiologists (ASA) physical status I to II. The exclusion criteria include the following: BMI≥35kg/m²; history of epilepsy or use of antiepileptic drugs; neuromuscular disorder(s); personal history or family history of malignant hyperthermia; allergies to sugammadex; NMBs or other medication(s) used during general anaesthesia; haemoglobin<110g/L; TceMEPs stimulation or recorded site infection; preoperative neurological dysfunction in both upper extremities; cardiac pacemaker; pregnancy and lactation. Patients will be excluded if they have used any other investigational drugs within 30 days of randomisation or have participated in another clinical trial within 30 days.

**Randomisation and blinding**

Written informed consent will be obtained during preoperative evaluation by an anaesthesiologist. See online supplemental file 1 for the patient informed consent. Subsequently, each patient will be randomly allocated to either the sugammadex group or control group. Randomisation will be performed by a computer-generated table. The allocation plan will be conducted using a variable block randomisation method at 1:1 to distribute the patients equally in each group. A designated staff who will neither be involved in anaesthesia management nor follow-up will perform recruitment as well as allocation randomisation sequence. This designated staff will implement the allocation sequence through opaque, sealed, and stapled envelopes.

Since the intervention in this clinical trial includes TOF monitoring which will be performed by anaesthesiologists, they will know the specific grouping information, but the neurophysiologists, neurosurgeons and the follow-up assessor will be blinded to the grouping.

**Intervention**

All patients will undergo neuromuscular monitoring with ulnar nerve stimulation using a closed-loop muscle relaxant infusion system (CLMRIS-I, Guangxi VERYARK...
near the ulnar nerve. The acceleromyograph transducer (CLMRIS-I, Guangxi VERYARK Technology Co., China) will be placed on the ventral aspect of the top of the thumb perpendicular to the movement of the thumb. The baseline TOF will be calibrated by a 5s and 50 Hz tetanic stimulation of ulnar nerve after administration of propofol prior to muscle relaxation. Subsequently, repetitive TOF stimulation will be conducted every 15s. All patients will receive a rocuronium infusion producing moderate blockade by the infusion system, which will be maintained by at least two twitches in TOF. The maintenance rate will start from 0.6µg/kg/min and subsequently adjusted up to 12µg/kg/min, and the bolus rate is 30µg/kg/min. Rocuronium infusion will be discontinued, and a bolus of sugammadex (2mg/kg) will be given while performing TcEMEPs in sugammadex group. Patients’ actual body weight will be used for the dosage of sugammadex. The same volume of saline will be given in the control group while performing TcEMEPs.

Anaesthesia regimen

No premedication will be administered before entering the operating room. The baseline characteristics will be collected before anaesthesia including date of birth, gender, height, weight, allergy history, medical history, diagnosis, type of surgery, preoperative motor function assessment and ASA physical status.

Standard ASA parameters will be monitored perioperatively, including blood pressure, ECG, pulse oxygen saturation, body temperature and end-tidal carbon dioxide partial pressure (ETCO₂). Anaesthesia induction and maintenance will be conducted with a target-controlled infusion device (Marsh model, Master TCI-Diprifusor, Fresenius, Brezins, France). A propofol target concentration of 6µg/mL and a remifentanil target concentration of 4ng/mL will be set to allow intubation. Additionally, 0.6mg/kg rocuronium will be given after loss of consciousness.

Tracheal intubation will be performed after the patient fails to register signals using TOF. Respiratory parameters will be adjusted according to arterial blood gas analysis to maintain PaCO₂ at 35–40 mm Hg. The tidal volume will be set at 6–8mL/kg, the respiratory rate will be set at 10–12 breaths/min. The infusion of propofol will be reduced to a target concentration of 3–6µg/mL to maintain a BIS (BIS Vista monitor, Aspect Medical Systems, Natick, MA) value of 40–50. The mean arterial pressure and heart rate (HR) will be maintained at a level of ±20% compared with baseline. If blood pressure increases over 20% from baseline, vasoactive drugs such as nicardipine and esmolol will be given. Dopamine will be given when blood pressure decreases to below 20% of baseline. Intraoperative body temperature will be maintained between 36°C and 37°C using an insulation blanket.

Acquisition of TcEMEPs

The acquisition of TcEMEPs has been described previously. Patients in both groups will be monitored with TcEMEPs (Nicolet Neurological Workstation, Endeavour CR, Madison, WI). To avoid the interference of surgery manipulation on thoracic or lumbar levels for lower limb muscles, recordings will be collected by measuring the myogenic responses from the upper extremity abductor pollicis brevis muscles using needle electrodes. The stimulus parameters for TcEMEPs will be a constant voltage with a stimulus pulse width of 0.3ms, with five pulses and an interstimulus interval of 2ms. The maximum stimulation intensity will be 200 V. The filter range is 300–3000 Hz, and the signal analysis time is 100 ms. Thirty minutes after induction of anaesthesia, constant voltage stimulation will begin at 100 V to obtain the TcEMEPs threshold voltage. The stimulus intensity will increase in steps of 20 V until the amplitudes (peak to peak) of TcEMEPs>50 µV are obtained. These voltage levels are considered as TcEMEPs threshold intensities for monitoring in surgery. The neurophysiologists will collect TcEMEP waveforms twice under the same stimulation threshold, if both of waveforms are more than 50 µV, which will be defined as ‘repeatable’ waveform. The success of TcEMEPs is defined as collecting repeatable and stable TcEMEPs waveforms (wave amplitude≥50 µV) examined by neurophysiologists who is blinded to the grouping. The latencies (duration between the starting point of stimulation to the peak of the first negative wave) and amplitudes of TcEMEPs in the upper extremities will be recorded at 5, 10, 20, 30 and 60 min after first performing of TcEMEPs.

See figure 1 for a flow diagram of the study.

![Figure 1: Consolidated standards of reporting trials flow diagram for this trial. TcEMEPs, transcranial motor-evoked potentials.](http://bmjopen.bmj.com/ BMJ Open: first published as 10.1136/bmjopen-2021-056571 on 2 May 2022. Downloaded from http://bmjopen.bmj.com on September 15, 2023 by guest. Protected by copyright.)
Follow-up

Follow-up examination will be performed 5 days after surgery by an anaesthesiologist blinded to the group allocation using the ‘sensory-motor profile awake scale’ (SMP-a). Any adverse events and complications before discharge from the hospital will be recorded.

Remedy

If the TceMEPs fail to record, the surgeons will be informed to check the surgery manipulation. The neurophysiologists will check the stimulating apparatus and stimulating conditions such as stimulus intensity, interpulse intervals and numbers of pulse trains. The anaesthesiologists will check the physiological parameters such as blood pressure, body temperature and positioning. The depth of anaesthesia will be adjusted to maintain a BIS value < 50 to avoid intraoperative awareness. If the failure of TceMEPs is caused by muscle relaxant, then sugammadex will be infused to maintain TOF ratio > 0.9. In the case of unexpected events such as body movement, the protocol will be stopped and the event will be recorded on the case report form.

Study endpoints

The primary endpoint of the study is the success rate of TceMEPs recording in the abductor pollicis brevis muscles of upper extremities 5 min after first performing of TceMEPs.

The secondary endpoints include the following:

1. Mean value of amplitudes of TceMEPs in the abductor pollicis brevis muscles of both upper extremities at 5, 10, 20, 30 and 60 min after first performing of TceMEPs.
2. Mean value of latencies of TceMEPs in the abductor pollicis brevis muscles of both upper extremities at 5, 10, 20, 30 and 60 min after first performing of TceMEPs.
3. The thresholds that are required to obtain a dependable TceMEPs response.
4. Peak respiratory pressures.
5. Adverse effects of sugammadex such as anaphylaxis including flushing, oedema, tachycardia and bronchospasm, arrhythmias (HR lower than 60 bpm), postprocedural pain, nausea and vomiting, fever (body temperature more than 37.3°C) and diarrhoea.
6. Incidence of body movement classified as either nociception-induced movement (defined as ‘coughing’ or reflexive limb movement temporally related to MEP stimulation) or excessive field movement (defined as grossly visible movement as determined by surgical and anaesthesia teams).
7. Recurrence of NMB defined as TOF ratio < 0.9 at time of extubation.

Data management

All paper versions of the original materials will be photographed and saved in an encrypted database. All electronic data will be stored in the electronic medical records of Beijing Tiantan Hospital. All procedures for evaluating endpoints will be filmed and saved.

Sample size calculation

The PASS V.15 software (NCSS, LLC, USA) is used to calculate the sample size based on the primary endpoint. According to a previous study, the success rate of TceMEPs is about 80% under pNMB, we hypothesise that success rate of obtaining recordable TceMEPs will reach 95% after muscle relaxant reversal by sugammadex.

Taking this into account, the sample size in each group should be 81 to achieve a power of 80% at a two-tailed significant level of 0.05, with a drop-out rate of 10%.

Statistical analysis

The statistical analysis will be performed by an independent statistician using SPSS V.18.0 (Somers, NY, USA). The data will be analysed on an intention-to-treat basis. Descriptive statistics of all variables describing the characteristics of the patients enrolled in the study and those excluded from the study will be analysed. All measurement data will be analysed for normal distribution and homogeneity of variance. Measurement data that show a normal distribution will be presented as the mean ± SD. Non-normal distribution data will be presented as medians. Categorical variables will be summarised by percentage and number of patients.

The mean value of amplitudes of TceMEPs in the abductor pollicis brevis muscles of both upper extremities 5 min after first performing of TceMEPs will be analysed by independent sample t-tests. The mean value of the amplitudes and latencies measured at different time points will also be analysed by independent sample t-tests. Repeated-measures analysis of variance will be used to check within-group differences at different time points. For categorical variables such as incidence of adverse effects and body movement, the χ² test or the Fisher exact test will be performed. A two-sided p value of less than 0.05 will be considered statistically significant. No interim analysis will be performed, and the study will be terminated after enrolment of the last patient.

Reporting of adverse events

All adverse events associated with this trial will be recorded and closely monitored until resolution or stabilisation or until it has been shown that study treatment is not the cause of the event. The principal investigator is responsible for reporting all adverse events. Once adverse events occur, it should be immediately reported to the research department and informed to the principal investigator to determine the severity of the adverse events.

Ethics and dissemination

The approval for the study was certificated by the Ethical Committee of Beijing Tiantan Hospital, Capital Medical University on 16 July 2021 (KY2021-082-02). The study was registered on clinicaltrials.gov on 25 October 2020 (NCT04608682). The study recruited the first patient on 16 August 2021, and the estimated study completion
date will be 30 December 2022. The findings of the study will be published in peer-reviewed journals and will be presented at national or international conferences.

See online supplemental file 2 for the Standard Protocol Items: Recommendations for Interventional Trials checklist.

DISCUSSION
The purpose of TcMEPs monitoring is to assess the functional integrity of motor pathways throughout the operative procedure to facilitate detection of motor dysfunction early enough to allow intervention before damage becomes irreversible. To the best of our knowledge, this is the first randomised controlled trial to evaluate the success rate of TcMEPs monitoring in patients undergoing spinal surgery on intraoperative reversal of muscle relaxant. The interpretation of TcMEPs can be affected by multiple factors such as hypothermia, hypotension, hypoxemia, electrolyte imbalance and depth of anaesthesia.\(^2\)\(^9\) These factors will be tightly controlled in our study.

NMB abolishes myogenic motor-evoked potentials and increases the risk of neurological injury when performing TcMEPs. Therefore, muscle relaxants should be omitted during TcMEPs monitoring.\(^3\) However, certain special concerns exist for anaesthesiologists relative to avoidance of muscle relaxants during the procedure. Some surgical procedures require extensive dissection to increase field visibility, such as the anterior transabdominal approach for lumbar spine surgery and posterior thoracic spine surgery.\(^19\) Unacceptable movements or coughs with TcMEPs monitoring in the absence of NMB have been observed in several studies.\(^9\)\(^20\) The increased risk of body movement can be controlled by a higher dosage of propofol and remifentanil. However, hyperalgesia caused by remifentanil should be considered. Additionally, increased depth of anaesthesia might lead to delayed emergence, hypotension and bradycardia requiring vasopressors.\(^3\) Moreover, high peak insufflation pressure could occur without NMB.

Under these circumstances, pNMB seems to be preferable to the surgical team. However, the partially paralysed patients require a higher stimulation intensity. Extremely high stimulus intensity can activate the deep subcortical motor pathways and bypass higher cortical levels, which might lead to the generation of MEPs from the deepening of the contralateral limbs despite cortical ischaemia. Therefore, the incidence of monitoring failure and false-positive will be increased.\(^9\) The feasibility of full NMB has been evaluated by Selner et al.\(^21\) Patients undergoing cervical or lumbar decompression received NMB by zero visible twitches from qualitative TOF can still successfully perform TcMEPs monitoring.

Theoretically, the availability of sugammadex makes it possible to use NMB during spinal surgery to improve surgical conditions without affecting TcMEPs monitoring. Sugammadex has been shown to be a safe and fast alternative for reversal of neuromuscular blocking induced by rocuronium in different clinical situations. However, to the best of our knowledge, there is no data on whether the sugammadex molecule itself has any interference on TcMEPs. Pavoni and Batistaki et al.\(^4\)\(^22\) demonstrated that sugammadex can produce rapid and complete reversal of profound and ‘deep’ residual rocuronium-induced NMB without neuromuscular recurrence during intraoperative mMEPs monitoring. However, it was the time from administration of sugammadex to the recovery of prerelaxation mMEPs amplitude was analysed, and our study will focus on the TcMEPs signals, that is, amplitudes and latencies after reversal of sugammadex. The sample sizes in those studies were both small, which limited their clinical value.

However, our study still has some limitations, to avoid the interference of surgery manipulation on thoracic or lumbar levels for lower limb muscles, we choose abductor pollicis brevis muscles to check the TcMEPs recording. This may limit the generalisation of our data to other muscle groups especially from lower limb muscles, due to the difference in recovery rate of each muscle. Besides, our study is a single-centred trial, future multicentre trial is needed to verify the effects of sugammadex on success rates of TcMEPs.

In summary, this parallel-group, randomised, controlled trial aims to assess whether the use of sugammadex is effective and safe for reversal of muscle relaxants during TcMEPs monitoring in spinal surgery. The features of the current study involve a strict randomised system, clear inclusion and exclusion criteria and a rigorous uniform protocol to manage haemodynamic and respiratory parameters and depth of anaesthesia in both groups. The findings of the study could serve as a reference for intraoperative use of sugammadex in TcMEPs monitoring during spinal surgery.

Correction notice This article has been corrected since it first published. Affiliation has been updated.

Contributors RH and HL conceived the primary idea of the study. All authors contributed to the writing of the protocol. BM and MJ drafted this paper in close cooperation with RH. The study will be executed by BM, MJ, HL, CW, FL, YZ and HQ. Data analysis will be performed by YZ. All authors have read and approved the final manuscript.

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