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Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential Monitoring in Patients Undergoing Spinal Surgery: Study Protocol for a Randomized Controlled Trial

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Abstract:

Introduction: Transcranial motor evoked potentials (TceMEPs) 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 neuromuscular blockade. This study aims to evaluate the success rate of intraoperative muscle relax reversal by sugammadex on intraoperative TceMEP monitoring.

Methods and analysis: We will conduct a single centre randomized 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 to 1. Total intravenous anaesthesia by propofol and remifentanil will be performed in both groups. In the sugammadex group, patients will receive continuous infusion of rocuronium to produce a blockade maintained for at least two twitches in Trian-of-four (TOF), rocuronium infusion will be discontinued and 2 mg/kg sugammadex will be infused while performing TceMEPs monitoring. In the control group, rocuronium infusion will be discontinued and the same volume of saline will be infused while performing TceMEPs monitoring. The primary aim of this study is to evaluate the success rate of TceMEPs monitoring 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, July 16, 2021 (KY2021-082-02). The study was registered on clincaltrials.gov on Oct 25, 2020 (NCT04608682). Our study might guide neuromuscular blockade plans in TceMEPs 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: ClinicalTrials.gov Identifier: NCT04608682.

Keywords: Sugammadex, Motor Evoked Potentials, Spinal Surgery; Neuromuscular Blockade; Success Rate

Strengths and limitations of this study

- Transcranial motor evoked potentials is conventionally performed without neuromuscular blockade because of its potential interference with neuromuscular junction and signal interpretation.
- The feasibility of transcranial motor evoked potentials interpretation was assessed during partial neuromuscular blockade in adult neurosurgical patients. However, partial neuromuscular blockade may interfere record of motor evoked potentials monitoring.
- Sugammadex is the first highly selective antagonist that binds to rocuronium and can rapidly and effectively reverse neuromuscular blockade. However, no strong evidence of prospective study exists that evaluates the use of sugammadex to reverse the effect of rocuronium during transcranial motor evoked potentials monitoring.
- This study is a randomized controlled trial to evaluate the success rate of intraoperative muscle relaxation reversal by sugammadex on intraoperative transcranial motor evoked potentials monitoring.

Background

Intraoperative neuromonitoring (IOM) uses a combination of motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPs) to test neural integrity during spinal surgery. This method is reliable 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 (TceMEPs), 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].

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[3]. 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[4], which consists of total intravenous anaesthesia using propofol and remifentanil without the use of NMB.

However, appropriate muscle relaxation optimizes 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)[5]. Kalkman maintained pNMB at T1 twitch height of 5–15%, whereas additional classification of pNMB aimed at T1 twitch height of 45–55% by van Dongen led to contrasting results[6, 7]. Liu et al has 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 TIVA. Nevertheless, the incidence of monitoring failure and false-positive results was increased under pNMB[8, 9].

Sugammadex is a modified γ-cyclodextrin derivative that selectively binds to NMB (rocuronium and vecuronium), which can encapsulate rocuronium and reverse the rocuronium-induced neuromuscular blockade at the neuromuscular junction[10]. 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) [11-13]. With these doses, it takes 2-3 minutes 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 [14].

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

Methods/design

Study design

This study is a prospective, single-centre, parallel-group, assessor-blinded, randomized 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 at ClinicalTrials.gov (NCT04608682) on October 25, 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 ≥35 kg/m^{-2}; 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 <110 g/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 randomization or have participated in another clinical trial within 30 days. See Table 1.

Table 1 Inclusion and exclusion criteria

Inclusion	Exclusion
1. Age range: 18–65 years old	1. BMI ≥35 kg/m-2
2. Thoracic or lumbar spinal surgery with TceMEPs monitoring	2. History of epilepsy or use of antiepileptic drugs
3. ASA physical status I to II	3. Neuromuscular disorder(s)
4. Sign informed consent	4. Personal history or family history of malignant hyperthermia
	5. Allergies to sugammadex; NMBs or other medication(s) used during general anaesthesia
	6. Haemoglobin <110 g/L
	7. TceMEPs stimulation or recorded site infection
	8. Preoperative neurological dysfunction in both upper extremities

	9. Cardiac pacemaker; Pregnant and lactating women

ASA, American Society of Anaesthesiologists physical status classification system; BMI, body mass index; NMB, neuromuscular blockade (NMB); TceMEPs, Transcranial motor evoked potentials.

Randomization and blinding

Written informed consent will be obtained during preoperative evaluation by an anaesthesiologist. Subsequently, each patient will be randomly allocated to either the sugammadex group or control group. Randomization will be performed by a computer-generated table. The allocation plan will be carried out using a variable block randomization method at 1:1 to distribute the patients equally in each group.

Since the intervention in this clinical trial includes TOF monitoring, the anaesthesiologists 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 Technology Co., Ltd, China.). The electrodes will be positioned near the ulnar nerve. The acceleromyographic transducer 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 5 s and 50 Hz tetanic stimulation of ulnar nerve after administration of propofol prior to muscle relaxation. Subsequently, repetitive TOF stimulation will be conducted every 15 s. 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 is 0.6 ug/kg/min, and the bolus rate is 30 ug/kg/min. Rocuronium infusion will be discontinued, and 2 mg/kg of sugammadex will be infused while performing TceMEPs in sugammadex group. The same volume of saline will be used in the control group while performing TceMEPs.

Anaesthesia regimen

No premedication will be administered before entering the operating room. Standard ASA parameters will be monitored perioperatively, including blood pressure, electrocardiogram, pulse

oxygen saturation, body temperature, and end-tidal carbon dioxide partial pressure ($ETCO_2$). 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 6 μg/mL and a remifentanil target concentration of 4 ng/mL will be set to allow intubation. Additionally, 0.6 mg/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 $PaCO_2$ at 35 to 40 mmHg. The infusion of propofol will be reduced to a target concentration of 3 to 6 ug/mL to maintain a BIS (BIS Vista monitor, Aspect Medical Systems, Natick, MA) value of 40 to 50. The mean arterial pressure (MAP) and heart rate (HR) will be maintained at a level of ± 20% compared to 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 and 37℃.

Acquisition of TceMEPs

The acquisition of TceMEPs has been described previously[4]. Patients in both groups will be monitored with TceMEPs (Nicolet Neurological Workstation, Endeavor CR, Madison, WI). Recordings will be collected by measuring the myogenic responses from the upper extremity abductor pollicis brevis muscles using needle electrodes. The filter range is 300 to 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 0) of TceMEPs > 50 uV are obtained. These voltage levels are considered as TceMEPs threshold intensities for monitoring in surgery. The success of TceMEPs is defined as collecting repeatable and stable TceMEPs waveforms (wave amplitude ≥ 5uv) under the same stimulation threshold examined by neurophysiologists. 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 minutes after first performing of TceMEPs.

See Figure 1 for a flow diagram of the study.

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)[15]. 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[16]. 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>90%. 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 monitoring in the abductor pollicis brevis muscles of upper extremities 5 minutes 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 minutes 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 minutes after first performing of TceMEPs.
3. Peak respiratory pressures and incidence of peak insufflation pressure of more than 25cmH_2O.
4. Adverse effects of sugammadex such as anaphylaxis, arrhythmias, postprocedural pain, nausea and vomiting, fever, and diarrhea, etc.
5. 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).
6. Recurrence of neuromuscular blockade at the end of surgery.
7. Motor function assessment using SMP-a 5 days after surgery.

8. Total bleeding volume during the surgery.

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 15 software (NCSS, LLC, USA) is used to calculate the sample size based on the primary endpoint. According to a previous study[5], the success rate of TceMEPs is about 80% under pNMB, we hypothesis success rate of TceMEPs will evaluate to 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 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 summarized by percentage and number of patients.

The mean value of amplitudes of TceMEPs in the abductor pollicis brevis muscles of both upper extremities 5 minutes after dura opening 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 ANOVA 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 chi-square 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 stabilization 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 July 16, 2021 (KY2021-082-02). The study was registered on clincaltrials.gov on October 25, 2020 (NCT04608682). The study recruited the first patient on August 16, 2021, and the estimated study completion date will be December 30, 2022.The findings of the study will be published in peer-reviewed journals and will be presented at national or international conferences.

Discussion

The purpose of TceMEPs 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 randomized controlled trial to evaluate the success rate of TceMEPs monitoring in patients undergoing spinal surgery on intraoperative reversal of muscle relaxant. The interpretation of TceMEPs can be affected by multiple factors such as hypothermia, hypotension, hypoxemia, electrolyte imbalance and depth of anaesthesia[17]. These factors will be tightly controlled in our study.

NMB abolishes myogenic motor-evoked potentials and increases the risk of neurological injury when performing TceMEPs. Therefore, muscle relaxants should be generally omitted during TceMEPs 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[17]. Unacceptable movements or coughs with TceMEPs monitoring in the absence of NMB have been observed in several studies[9, 18]. 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[8]. Moreover, high peak insufflation pressure could occur without NMB.

Under these circumstances, pNMB seems to be preferable to the surgical team. However, the partially paralyzed patients require a higher stimulation intensity. Very 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 ischemia. 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[19]. Patients undergoing cervical or lumbar decompression received NMB by 0 visible twitches from qualitative TOF can still successfully perform TceMEPs monitoring.

Theoretically, the availability of sugammadex makes it possible to use NMB during spinal surgery to improve surgical conditions without affecting TceMEPs monitoring. Sugammadex has

been shown to be a safe and fast alternative for reversal of neuromuscular blocking induced by rocuronium in different clinical situations. Pavoni and Batistaki et al[20]·[21] 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 TceMEPs signals, i.e., amplitudes and latencies after reversal of sugammadex. The sample sizes in those studies were both small, which limited their clinical value.

In summary, this parallel group, randomized, controlled trial aims to assess whether use of sugammadex is effective and safe for reversal of muscle relaxants during TceMEPs monitoring in spinal surgery. The features of the current study involve a strict randomized system, clear inclusion and exclusion criteria and a rigorous uniform protocol to manage hemodynamic 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 TceMEPs monitoring during spinal surgery.

Ethics approval and consent to participate

The trial has been approved by the Institutional Review Board of Beijing Tiantan Hospital on July 16, 2021 (KY2021-082-02). Written informed consent was obtained from all participants.

Patient and Public Involvement

Patients and the public were not involved in the trial design. Participants will have access to the findings of the study on request.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors have no potential conflicts of interest to declare with respect to the research, authorship, and/or publication of this article.

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Author contributions

RH and HL conceived the primary idea of the study. All authors contributed to the writing of the protocol. BM, MJ wrote 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.

List of tables and figures

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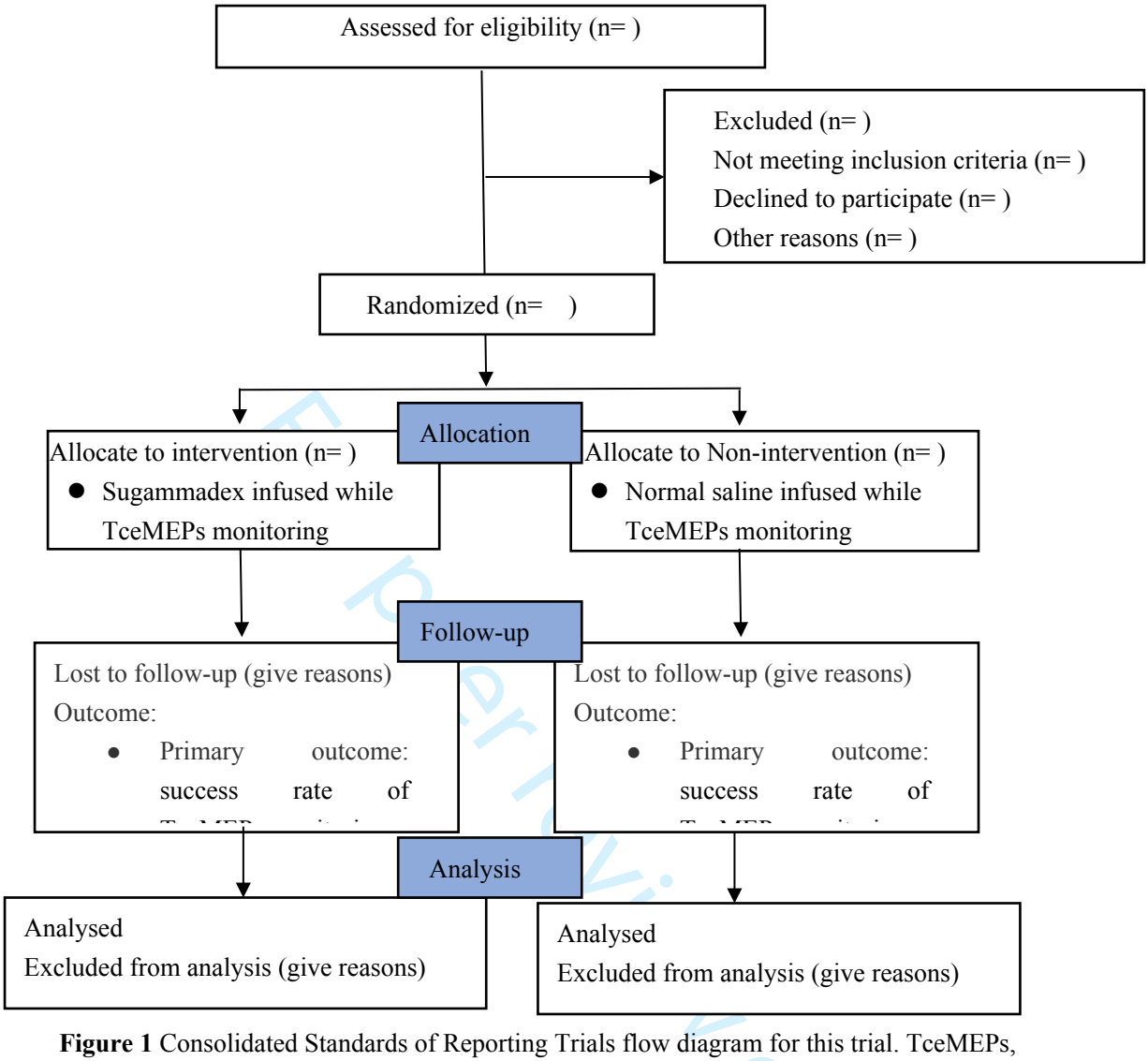

Figure 1 Consolidated Standards of Reporting Trials flow diagram for this trial. TceMEPs, Transcranial motor evoked potentials.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2/17
	2b	All items from the World Health Organization Trial Registration Data Set	2/17
Protocol version	3	Date and version identifier	/
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	11
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____/_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____3-4_____
	6b	Explanation for choice of comparators	_____3-4_____
Objectives	7	Specific objectives or hypotheses	_____4_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____5_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____5_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	____5_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____5-6____

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____7___
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____/____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____7_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____7-8_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____/_____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____8_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____/_____

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5-6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5-7

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____ 8____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____8-9____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____8-9____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____8-9____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____/_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____/_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____9____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____/_____

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	/
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	/
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	/
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9

	31b	Authorship eligibility guidelines and any intended use of professional writers	_____/_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____9_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____/_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____/_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential Recording in Patients Undergoing Spinal Surgery: Study Protocol for a Randomized Controlled Trial

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Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential recording in Patients Undergoing Spinal Surgery: Study Protocol for a Randomized Controlled Trial

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Abstract:

Introduction: Transcranial motor evoked potentials (TceMEPs) 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 neuromuscular blockade. This study aims to evaluate the success rate of intraoperative muscle relax reversal by sugammadex on intraoperative TceMEP recording.

Methods and analysis: We will conduct a single centre randomized 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 to 1. Total intravenous anaesthesia by propofol and remifentanil will be performed in both groups. In the sugammadex group, patients will receive continuous infusion of rocuronium to produce a blockade maintained for at least two twitches in Train-of-four (TOF), rocuronium infusion will be discontinued and 2 mg/kg sugammadex will be given while performing TceMEPs monitoring. In the control group, rocuronium infusion will be discontinued and the same volume of saline will be infused while performing TceMEPs monitoring. The primary aim of this study is to evaluate the success rate of TceMEPs 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, July 16, 2021 (KY2021-082-02). The study was registered on clincaltrials.gov on Oct 25, 2020 (NCT04608682). Our study might guide neuromuscular blockade plans in TceMEPs 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: ClinicalTrials.gov Identifier: NCT04608682.

Keywords: Sugammadex, Motor Evoked Potentials, Spinal Surgery; Neuromuscular Blockade; Success Rate

Strengths and limitations of this study

- Partial neuromuscular blockade may interfere record of motor evoked potentials monitoring
- Sugammadex is the first highly selective antagonist that binds to rocuronium and can rapidly and effectively reverse neuromuscular blockade
- This study is a randomized controlled trial to evaluate the success rate of intraoperative muscle relaxation reversal by sugammadex on intraoperative transcranial motor evoked potentials recording
- The abductor pollicis brevis muscles are chosen to check the TceMEPs recording results, this may limit the generalization of our data to other muscle groups especially from lower limb muscles

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 (TceMEPs), 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].

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[3]. 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[4], which consists of total intravenous anaesthesia using propofol and remifentanil without the use of NMB.

However, appropriate muscle relaxation optimizes 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[5]. 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)[6]. Kalkman maintained pNMB at T1 twitch height of 5–15%, whereas additional classification of pNMB aimed at T1 twitch height of 45–55% by van Dongen led to contrasting results[7 8]. Liu et al has 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 TIVA. Nevertheless, the incidence of monitoring failure and false-positive results was increased under pNMB[5 9].

Sugammadex is a modified γ-cyclodextrin derivative that selectively binds to NMB (rocuronium and vecuronium), which can encapsulate rocuronium and reverse the rocuronium-induced neuromuscular blockade at the neuromuscular junction[10]. 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) [11-14]. With these doses, it takes 2-3 minutes 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 [15].

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 randomized controlled trial to compare the success rate of TceMEPs recording under partial NMB and no NMB reversed by sugammadex. We hypothesize 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, randomized 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 at ClinicalTrials.gov (NCT04608682) on October 25, 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 ≥35 kg/m^2; 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 <110 g/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 randomization or have participated in another clinical trial within 30 days. See Table 1.

Randomization and blinding

Written informed consent will be obtained during preoperative evaluation by an anaesthesiologist. See Supplementary file 1 for the patient informed consent. Subsequently, each patient will be randomly allocated to either the sugammadex group or control group. Randomization will be performed by a computer-generated table. The allocation plan will be conducted using a variable block randomization 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 randomization 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 Technology Co., Ltd, China.). The electrodes will be positioned near the ulnar nerve. The acceleromyograph transducer 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 5 s and 50 Hz tetanic stimulation of ulnar nerve after administration of propofol prior to muscle relaxation. Subsequently, repetitive TOF stimulation will be conducted every 15 s. 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 0.6 ug/kg/min and subsequently adjusted up to 12 ug/kg/min, and the bolus rate is 30 ug/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, past medical history, diagnosis, type of surgery, preoperative motor function assessment and ASA physical status.

Standard ASA parameters will be monitored perioperatively, including blood pressure, electrocardiogram, pulse oxygen saturation, body temperature, and end-tidal carbon dioxide partial pressure ($ETCO_2$). 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 6 μg/mL and a remifentanil target concentration of 4 ng/mL will be set to allow intubation. Additionally, 0.6 mg/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 $PaCO_2$

at 35 to 40 mmHg. 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 to 6 ug/mL to maintain a BIS (BIS Vista monitor, Aspect Medical Systems, Natick, MA) value of 40 to 50. The mean arterial pressure (MAP) and heart rate (HR) will be maintained at a level of ± 20% compared to 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 and 37℃ using an insulation blanket.

Acquisition of TceMEPs

The acquisition of TceMEPs has been described previously[4]. Patients in both groups will be monitored with TceMEPs (Nicolet Neurological Workstation, Endeavor 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 0.3 ms, with five pulses and an interstimulus interval of 2 ms. The maximum stimulation intensity will be 200V. The filter range is 300 to 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 uV are obtained. These voltage levels are considered as TceMEPs threshold intensities for monitoring in surgery. The neurophysiologists will collect TceMEPs waveforms twice under the same stimulation threshold, if both of waveforms are more than 50uv, which will be defined as “repeatable” waveform. The success of TceMEPs is defined as collecting repeatable and stable TceMEPs waveforms (wave amplitude ≥ 50uv) 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 minutes after first performing of TceMEPs.

See Figure 1 for a flow diagram of the study.

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)[16]. 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[17]. 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 TOFr>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 minutes 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 minutes 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 minutes after first performing of TceMEPs.
3. The thresholds that are required to obtain a dependable TceMEPs response.
4. Peak respiratory pressures and incidence of peak insufflation pressure of more than 25cmH_2O.
5. Adverse effects of sugammadex such as anaphylaxis (including flushing, oedema, tachycardia and bronchospasm), arrhythmias (heart rate lower than 60bpm), postprocedural pain, nausea and vomiting, fever (body temperature more than 37.3℃), and diarrhea, etc[18].
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 neuromuscular blockade defined as TOFr < 0.9 at time of extubation.
8. Motor function assessment using SMP-a 5 days after surgery.
9. Total bleeding volume during the surgery.

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 15 software (NCSS, LLC, USA) is used to calculate the sample size based on the primary endpoint. According to a previous study[6], the success rate of TceMEPs is about 80% under pNMB, we hypothesize 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 eighty-one 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 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 summarized by percentage and number of patients.

The mean value of amplitudes of TceMEPs in the abductor pollicis brevis muscles of both upper extremities 5 minutes 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 ANOVA 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 chi-square 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 stabilization 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 July 16, 2021 (KY2021-082-02). The study was registered on clincaltrials.gov on October 25, 2020 (NCT04608682). The study recruited the first patient on August 16, 2021, and the estimated study completion date will be December 30, 2022.The findings of the study will be published in peer-reviewed journals and will be presented at national or international conferences.

See Supplementary file 2 for the SPIRIT checklist.

Discussion

The purpose of TceMEPs 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 randomized controlled trial to evaluate the success rate of TceMEPs monitoring in patients undergoing spinal surgery on intraoperative reversal of muscle relaxant. The interpretation of TceMEPs can be affected by multiple factors such as hypothermia, hypotension, hypoxemia, electrolyte imbalance and depth of anaesthesia[19]. These factors will be tightly controlled in our study.

NMB abolishes myogenic motor-evoked potentials and increases the risk of neurological injury when performing TceMEPs. Therefore, muscle relaxants should be omitted during TceMEPs 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 TceMEPs 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[5]. Moreover, high peak insufflation pressure could occur without NMB.

Under these circumstances, pNMB seems to be preferable to the surgical team. However, the partially paralyzed 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 ischemia. 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 TceMEPs monitoring.

Theoretically, the availability of sugammadex makes it possible to use NMB during spinal surgery to improve surgical conditions without affecting TceMEPs monitoring. Sugammadex has

been shown to be a safe and fast alternative for reversal of neuromuscular blocking induced by rocuronium in different clinical situations. Pavoni and Batistaki et al[14,22] 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 TceMEPs signals, i.e., 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 limitation, 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 TceMEPs recording results. This may limit the generalization 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 TceMEPs.

In summary, this parallel group, randomized, controlled trial aims to assess whether use of sugammadex is effective and safe for reversal of muscle relaxants during TceMEPs monitoring in spinal surgery. The features of the current study involve a strict randomized system, clear inclusion and exclusion criteria and a rigorous uniform protocol to manage hemodynamic 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 TceMEPs monitoring during spinal surgery.

Ethics approval and consent to participate

The trial has been approved by the Institutional Review Board of Beijing Tiantan Hospital on July 16, 2021 (KY2021-082-02). Written informed consent will be obtained from all participants.

Patient and Public Involvement

Patients and the public were not involved in the trial design. Participants will have access to the findings of the study on request.

Consent for publication

Written informed consent for publication will be obtained from all participants.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors have no potential conflicts of interest to declare with respect to the research, authorship, and/or publication of this article.

Funding

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Author contributions

RH and HL conceived the primary idea of the study. All authors contributed to the writing of the protocol. BM, 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.

List of tables and figures

References

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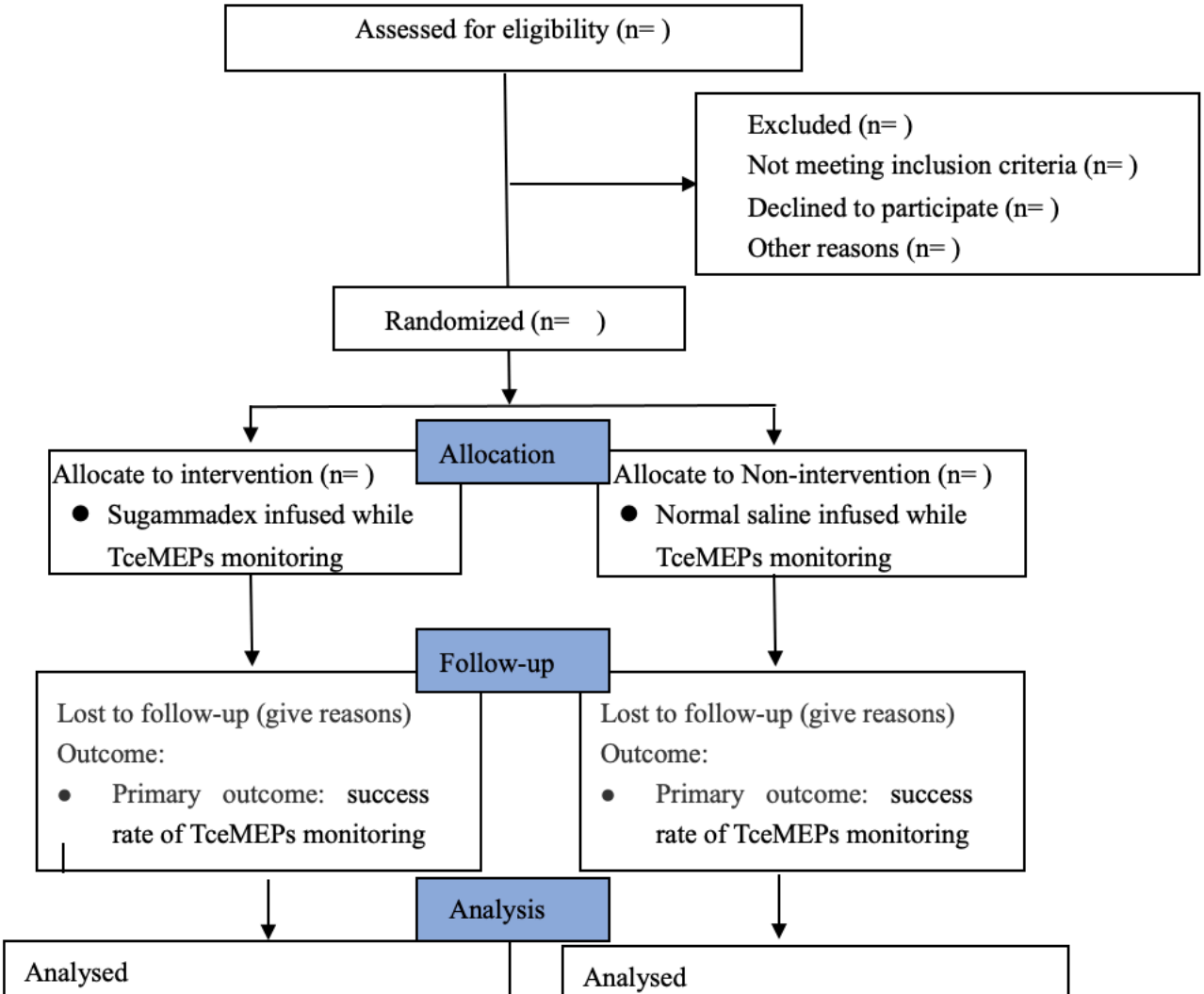
Assessed for eligibility (n=)
Excluded (n=)
Not meeting inclusion criteria (n=)
Declined to participate (n=)
Other reasons (n=)
Randomized (n=)
Allocation
Allocate to intervention (n=)
Sugammadex infused while TceMEPs monitoring
Allocate to Non-intervention (n=)
Normal saline infused while TceMEPs monitoring
Follow-up
Lost to follow-up (give reasons)
Outcome:
Primary outcome: success rate of TceMEPs monitoring
Lost to follow-up (give reasons)
Outcome:
Primary outcome: success rate of TceMEPs monitoring
Analysis
Analysed
Excluded from analysis (give reasons)
Analysed
Excluded from analysis (give reasons)

INFORMED CONSENT

Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential recording in Patients Undergoing Spinal Surgery

Project entrust organization: Beijing Tiantan Hospital

Contract Research Organization: N/A

Version : 2.0

2nd, June, 2021

INFORMATION SHEET

You will receive ***thoracic or lumbar spinal surgery***. We would like to invite you to participate our study, which is ***" Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential recording in Patients Undergoing Spinal Surgery"***, to evaluate the success rate of intraoperative muscle relax reversal by sugammadex on intraoperative TceMEP recording. This study is approved by Ethics Committee of Beijing Tiantan Hospital of Capital Medical University.During our study, we will follow the Declaration of Helsinki.

Before you decide whether participate this clinical trial, please take time to review this information carefully. This form describes the purpose, procedure, study duration, risks, and possible benefits of participating the study. You may also wish to talk to others, including your friends, family, or discuss with your anesthesiologist about your participation in this study.

1. PURPOSE of THIS STUDY

Intraoperative neuromonitoring (IOM) uses a combination of motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPs) to test neural integrity during spinal surgery. This method is reliable and validated for assessing spinal cord function. The Transcranial motor evoked potentials monitoring (TceMEPs) signals are exquisitely sensitive to neuromuscular blockade (NMB), the use of NMB is avoided except during intubation. However, appropriate muscle relaxation optimizes anaesthetic management, facilitates surgery, and prevents patient movement. Sugammadex is a modified γ-cyclodextrin derivative that selectively binds to NMB (rocuronium and vecuronium), which can reverse the rocuronium-induced neuromuscular blockade at the neuromuscular junction. The efficacy of reversing various levels of rocuronium block has been confirmed by multiple studies. Therefore, this study is a trial to compare the success rate of TceMEPs recording under partial NMB and no NMB reversed by sugammadex in spinal surgery.

2. NUMBER of PARTICIPANTS

In total, 162 patients will be included in the study.

3. WHO WILL PARTICIPANT IN THIS STUDY

- Age range from 18 to 65 years old
- American Society of Anaesthesiologists (ASA) physical status I to II

4. WHO SHOULD NOT PARTICIPATE in the STUDY

If you have following condition, you should not participate in the study:

- BMI ≥35 kg/m-2
- 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 <110 g/L
- TceMEPs stimulation or recorded site infection

- Preoperative neurological dysfunction in both upper extremities
- Cardiac pacemaker
- Pregnancy and lactation
- Any other investigational drugs used within 30 days of randomization or participated in another clinical trial within 30 days.

5. DURATION OF THIS STURY

This study will only be conducted during your hospital stay. You will be followed up at 2h, 24h, 48h, 72h after surgery for any adverse reactions, and your motor function will be assessed.

You can opt out of the research at any time without losing any benefits you should have received. However, if you decide to withdraw from this study during the study, we encourage you to consult with your doctor first. Considering your security issues, there may be a related check after you log out.

6. PROCESS OF THIS STUDY

If you are willing to participate in this study, your doctor will learn about your medical history, ask about your current disease, and current treatment medications to further confirm whether you are suitable for participating in this study.

If you are willing to participate in this study, during the general anesthesia of the operation, you have a half chance of using the closed-loop muscle relaxant injection system to maintain a moderate partial muscle relaxant and discontinue the muscle relaxants at the beginning of the key steps of the operation. There is also a one-half possibility of using a closed-loop muscle relaxant injection system to maintain a moderate partial muscle relaxant. At the beginning of the key steps of the operation, the muscle relaxant is discontinued, and the specific muscle relaxant antagonist is used at the same time. Later, the neurophysiologists will monitor your motor function to determine whether the operation will damage your motor function.

The day before your scheduled surgery, the researcher will determine whether you meet the inclusion-exclusion criteria of this study based on your disease and current status. If you agree to participate in the research, we will interview your medical details. After 2h, 24h, 48h, 72h, the researcher will examine your condition again. All visits will not cause you any harm. Participation in this study does not require changes to your surgical methods and postoperative treatment. Except for randomly entering a study group and receiving different administration methods of muscle relaxants, other anaesthesia management will not be affected in any way. Both medication regimens are safe. If you enter any research group, we will try your best to ensure that your surgery goes smoothly.

7. POSSIBLE BENEFITS of PARTICIPATING in the STUDY

The depth of anaesthesia and the degree of muscle relaxation will be under our strict monitoring to ensure the appropriate depth of anaesthesia and the success rate and accuracy of monitoring of TceMEPs during the operation. In addition, we will use the muscle relaxant antagonist Sugammadex free of charge for all subjects who use muscle relaxants after the operation, which will significantly reduce the occurrence of postoperative muscle relaxation and reduce complications related to muscle relaxation. The results obtained from this study may guide the use and management of intraoperative muscle relaxants in the future and bring benefits to patients undergoing similar operations.

8. POSSIBLE ADVERSE REACTIONS, RISKS and DISCOMFORT, INCONVENIENCES of PARTICIPATING in the STUDY

The adverse reactions of Sugammadex include nausea and vomiting, hypertension, and tachycardia. In this study, the dosage of Sugammadex is small and will not cause obvious adverse reactions. We have also formulated a detailed response plan if nausea and vomiting occur after surgery, you will be given antiemetic drugs; hypertension and tachycardia can be relieved by giving antihypertensive drugs.

If antagonistic drugs are not used during surgery, there may be a risk of failure in motor evoked potential monitoring. For this situation we have formulated the following remedy measures: ① Notify the surgeon and adjust the operation manipulation that may cause the failure of TceMEPs monitoring; ② Monitor the degree of muscle relaxation, and give appropriate amount of Sugammadex to maintain TOFr≥90%③Correct TceMEPs monitoring technical parameters, such as stimulation intensity, stimulation interval time and number of stimulation strings, etc.; ④ Correct Physiological parameter abnormalities that may occur during the operation, such as blood pressure, hemoglobin concentration, body temperature, arterial carbon dioxide partial pressure and body position, etc.; ⑤Adjust the depth of anesthesia under the guidance of the BIS value, and ensure that the BIS is ≤50 to avoid intraoperative awareness. The above plan will ensure your safety and the smooth progress of the operation.

If your health does suffer from research-related damage due to participation in this research, please notify the doctor immediately, who will be responsible for taking appropriate treatment measures for you. The sponsor, Beijing Tiatan Hospital, will bear the cost of treatment and provide you with corresponding financial compensation in accordance with relevant national regulations.Even if you have signed this informed consent form, you still retain all your legal rights.

9. OTHER TREATMENT CHOICE

If you do not participate in this study, you can choose your anesthesia treatment according to your anesthesiologist's suggestion.

10. YOU MAY VOLUNTARILY CHOOSE TO PARTICIPATE in the STUDY and WITHDRAW from the STUDY

Whether to participate in the study is entirely up to you. You may refuse to participate in the study or withdraw from the study at any time during the study, which will not affect your relationship with your doctor or affect your medical service or other benefits.

Before making decision, you can discuss with your family or friend， or you can talk with your doctor for any question, until you fully understand this study.

11. RELATED EXPENSES

Anesthetic drugs and surgical procedures are not free of charge. If you combine the treatment and examination required for other diseases, and if the treatment fails, the cost of changing to other treatment is not free of charge. If any medical expense happened due to adverse event, you will be exempted from the charge.

12. CONFIDENTIALITY of PERSONAL INFORMATION

Your medical records (study records /CRF, lab sheets, etc.) will be kept intact at the hospital. Your doctor will record the results of tests and other tests on your medical record. Researchers, ethics committees, and drug regulators will be allowed access to your medical records. Any public reports on the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical data within the law.

13. HOW TO GET MORE INFORMATION?

You can ask any questions about this study at any time and get answers. Your anesthesiologist will be ready to answer any of your questions before, during and after the study.

14. HOW THE STUDY MAY EFFECT YOUR LIFE?

You may feel the visit and examination uncomfortable and special arrangement is needed. You can consult your doctor in any steps of the study.

15. CONSULTING

If you have any related questions, please contact Dr. Jian Minyu (phone: 010-59976656 or cell phone: 13522550438).

If you have any concerns about your personal benefits, or you want to complain or express your concerns about the study, please contact the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (phone：010-59975178, email: ttyyirb@163.com).

SINGATURE PAGE OF AGREEMENT

Study title: Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential recording in Patients Undergoing Spinal Surgery

Principal Investigator: Ruquan Han, Beijing Tiantan Hospital, CMU

DECLARATION of CONSENT

I have read the introduction about the study above and have the opportunity to discuss with doctors and ask the questions about the study. All my questions have been answered satisfactorily.

I am aware of the possible risk and benefits of participating in this study. I know that participating in the study is voluntary. I have taken it into full consideration, and known that:

- I can ask my doctor for more information at any time.
- I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

I am also aware that if I withdraw from the study, especially if I withdraw due to medication, it will be of great benefit to the whole study if I tell my doctor about my condition and complete the corresponding physical examination and physical and chemical inspection.

If I need to take any other medication due to a change in my condition, I will consult my doctor beforehand or tell him afterwards truthfully.

I agree that the ethics committee of the drug regulatory authority or the representative of the sponsor may have access to my research information.

I will be provided with a signed and dated copy of the informed consent.

In the end, I agreed to participate in the study and promised to follow my doctors' advice as much as possible.

Signature of patient/legal relative:_____

Relation: _____

Date: _____ **(yyyy/mm/dd)**

I confirm that I have explained the details of the trial to the patients, including its rights and possible benefits and risks, and have given them a signed copy of the informed consent.

Signature of doctor:_____

Date: _____ **(yyyy/mm/dd)**

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2/17
	2b	All items from the World Health Organization Trial Registration Data Set	2/17
Protocol version	3	Date and version identifier	/
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	11
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____/_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____3-4_____
	6b	Explanation for choice of comparators	_____3-4_____
Objectives	7	Specific objectives or hypotheses	_____4_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____5_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____5_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	____5_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____5-6____

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____7___
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____/____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____7_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____7-8_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____/_____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____8_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____/_____

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5-6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5-7

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____ 8____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____8-9____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____8-9____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____8-9____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____/_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____/_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____9____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____/_____

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	/
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	/
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	/
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9

	31b	Authorship eligibility guidelines and any intended use of professional writers	_____/_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____9_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____/_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____/_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential Recording in Patients Undergoing Spinal Surgery: Study Protocol for a Randomized Controlled Trial

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Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential recording in Patients Undergoing Spinal Surgery: Study Protocol for a Randomized Controlled Trial

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Abstract:

Introduction: Transcranial motor evoked potentials (TceMEPs) 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 neuromuscular blockade. This study aims to evaluate the success rate of intraoperative muscle relax reversal by sugammadex on intraoperative TceMEP recording.

Methods and analysis: We will conduct a single centre randomized 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 to 1. Total intravenous anaesthesia by propofol and remifentanil will be performed in both groups. In the sugammadex group, patients will receive continuous infusion of rocuronium to produce a blockade maintained for at least two twitches in Train-of-four (TOF), rocuronium infusion will be discontinued and 2 mg/kg sugammadex will be given while performing TceMEPs monitoring. In the control group, rocuronium infusion will be discontinued and the same volume of saline will be infused while performing TceMEPs monitoring. The primary aim of this study is to evaluate the success rate of TceMEPs 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, July 16, 2021 (KY2021-082-02). The study was registered on clincaltrials.gov on Oct 25, 2020 (NCT04608682). Our study might guide neuromuscular blockade plans in TceMEPs 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: ClinicalTrials.gov Identifier: NCT04608682.

Keywords: Sugammadex, Motor Evoked Potentials, Spinal Surgery; Neuromuscular Blockade; Success Rate

Strengths and limitations of this study

- This study is a randomized controlled trial to evaluate the success rate of intraoperative muscle relaxation reversal by sugammadex on intraoperative transcranial motor evoked potentials recording under partial NMB or no NMB
- This study has a strict randomized system, clear inclusion and exclusion criteria and a rigorous uniform protocol to manage hemodynamic and respiratory parameters and depth of anaesthesia in both groups
- The abdductor pollicis brevis muscles are chosen to check the TceMEPs recording results, this may limit the generalization of our data to other muscle groups especially from lower limb muscles

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 (TceMEPs), 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].

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[3]. 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[4], which consists of total intravenous anaesthesia using propofol and remifentanil without the use of NMB.

However, appropriate muscle relaxation optimizes 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[5]. 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)[6]. Kalkman maintained pNMB at T1 twitch height of 5–15%, whereas additional classification of pNMB aimed at T1 twitch height of 45–55% by van Dongen led to contrasting results[7 8]. Liu et al has 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 TIVA. Nevertheless, the incidence of monitoring failure and false-positive results was increased under pNMB[5 9].

Sugammadex is a modified γ-cyclodextrin derivative that selectively binds to NMB (rocuronium and vecuronium), which can encapsulate rocuronium and reverse the rocuronium-induced neuromuscular blockade at the neuromuscular junction[10]. 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) [11-14]. With these doses, it takes 2-3 minutes 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 [15].

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 randomized controlled trial to compare the success rate of TceMEPs recording under partial NMB and no NMB reversed by sugammadex. We hypothesize 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, randomized 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 at ClinicalTrials.gov (NCT04608682) on October 25, 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 ≥35 kg/m^2; 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 <110 g/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 randomization or have participated in another clinical trial within 30 days.

Randomization and blinding

Written informed consent will be obtained during preoperative evaluation by an anaesthesiologist. See Supplementary file 1 for the patient informed consent. Subsequently, each patient will be randomly allocated to either the sugammadex group or control group. Randomization will be performed by a computer-generated table. The allocation plan will be conducted using a variable block randomization 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 randomization 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 Technology Co., Ltd, China.). The electrodes will be positioned near the ulnar nerve. The acceleromyograph transducer (CLMRIS-I，Guangxi VERYARK Technology Co., Ltd, 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 5 s and 50 Hz tetanic stimulation of ulnar nerve after administration of propofol prior to muscle relaxation. Subsequently, repetitive TOF stimulation will be conducted every 15 s. 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 0.6 ug/kg/min and subsequently adjusted up to 12 ug/kg/min, and the bolus rate is 30 ug/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, past medical history, diagnosis, type of surgery, preoperative motor function assessment and ASA physical status.

Standard ASA parameters will be monitored perioperatively, including blood pressure, electrocardiogram, pulse oxygen saturation, body temperature, and end-tidal carbon dioxide partial pressure ($ETCO_2$). 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 6 μg/mL and a remifentanil target concentration of 4 ng/mL will be set to allow intubation. Additionally, 0.6 mg/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 $PaCO_2$

at 35 to 40 mmHg. 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 to 6 ug/mL to maintain a BIS (BIS Vista monitor, Aspect Medical Systems, Natick, MA) value of 40 to 50. The mean arterial pressure (MAP) and heart rate (HR) will be maintained at a level of ± 20% compared to 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 and 37℃ using an insulation blanket.

Acquisition of TceMEPs

The acquisition of TceMEPs has been described previously[4]. Patients in both groups will be monitored with TceMEPs (Nicolet Neurological Workstation, Endeavor 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 0.3 ms, with five pulses and an interstimulus interval of 2 ms. The maximum stimulation intensity will be 200V. The filter range is 300 to 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 uV are obtained. These voltage levels are considered as TceMEPs threshold intensities for monitoring in surgery. The neurophysiologists will collect TceMEPs waveforms twice under the same stimulation threshold, if both of waveforms are more than 50uv, which will be defined as “repeatable” waveform. The success of TceMEPs is defined as collecting repeatable and stable TceMEPs waveforms (wave amplitude ≥ 50uv) 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 minutes after first performing of TceMEPs.

See Figure 1 for a flow diagram of the study.

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)[16]. 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[17]. 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 TOFr>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 minutes 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 minutes 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 minutes after first performing of TceMEPs.
3. The thresholds that are required to obtain a dependable TceMEPs response.
4. Peak respiratory pressures and incidence of peak insufflation pressure of more than 25cmH_2O.
5. Adverse effects of sugammadex such as anaphylaxis (including flushing, oedema, tachycardia and bronchospasm), arrhythmias (heart rate lower than 60bpm), postprocedural pain, nausea and vomiting, fever (body temperature more than 37.3℃), and diarrhea, etc[18].
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 neuromuscular blockade defined as TOFr < 0.9 at time of extubation.
8. Motor function assessment using SMP-a 5 days after surgery.
9. Total bleeding volume during the surgery.

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 15 software (NCSS, LLC, USA) is used to calculate the sample size based on the primary endpoint. According to a previous study[6], the success rate of TceMEPs is about 80% under pNMB, we hypothesize 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 eighty-one 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 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 summarized by percentage and number of patients.

The mean value of amplitudes of TceMEPs in the abductor pollicis brevis muscles of both upper extremities 5 minutes 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 ANOVA 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 chi-square 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 stabilization 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 July 16, 2021 (KY2021-082-02). The study was registered on clincaltrials.gov on October 25, 2020 (NCT04608682). The study recruited the first patient on August 16, 2021, and the estimated study completion date will be December 30, 2022.

See Supplementary file 2 for the SPIRIT checklist.

Discussion

The purpose of TceMEPs 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 randomized controlled trial to evaluate the success rate of TceMEPs monitoring in patients undergoing spinal surgery on intraoperative reversal of muscle relaxant. The interpretation of TceMEPs can be affected by multiple factors such as hypothermia, hypotension, hypoxemia, electrolyte imbalance and depth of anaesthesia[19]. These factors will be tightly controlled in our study.

NMB abolishes myogenic motor-evoked potentials and increases the risk of neurological injury when performing TceMEPs. Therefore, muscle relaxants should be omitted during TceMEPs 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 TceMEPs 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[5]. Moreover, high peak insufflation pressure could occur without NMB.

Under these circumstances, pNMB seems to be preferable to the surgical team. However, the partially paralyzed 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 ischemia. 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 TceMEPs monitoring.

Theoretically, the availability of sugammadex makes it possible to use NMB during spinal surgery to improve surgical conditions without affecting TceMEPs 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 our knowledge, there is no data on whether the sugammadex molecule itself has any interference on TceMEPs. Pavoni and Batistaki et al[14,22] 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 TceMEPs signals, i.e., 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 limitation, 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 TceMEPs recording results. This may limit the generalization 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 TceMEPs.

In summary, this parallel group, randomized, controlled trial aims to assess whether use of sugammadex is effective and safe for reversal of muscle relaxants during TceMEPs monitoring in spinal surgery. The features of the current study involve a strict randomized system, clear inclusion and exclusion criteria and a rigorous uniform protocol to manage hemodynamic 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 TceMEPs monitoring during spinal surgery.

Ethics approval and consent to participate

The trial has been approved by the Institutional Review Board of Beijing Tiantan Hospital on July 16, 2021 (KY2021-082-02). Written informed consent will be obtained from all participants.

Patient and Public Involvement

Patients and the public were not involved in the trial design. Participants will have access to the findings of the study on request.

Consent for publication

Written informed consent for publication will be obtained from all participants.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors have no potential conflicts of interest to declare with respect to the research, authorship, and/or publication of this article.

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Author contributions

RH and HL conceived the primary idea of the study. All authors contributed to the writing of the protocol. BM, 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.

List of tables and figures

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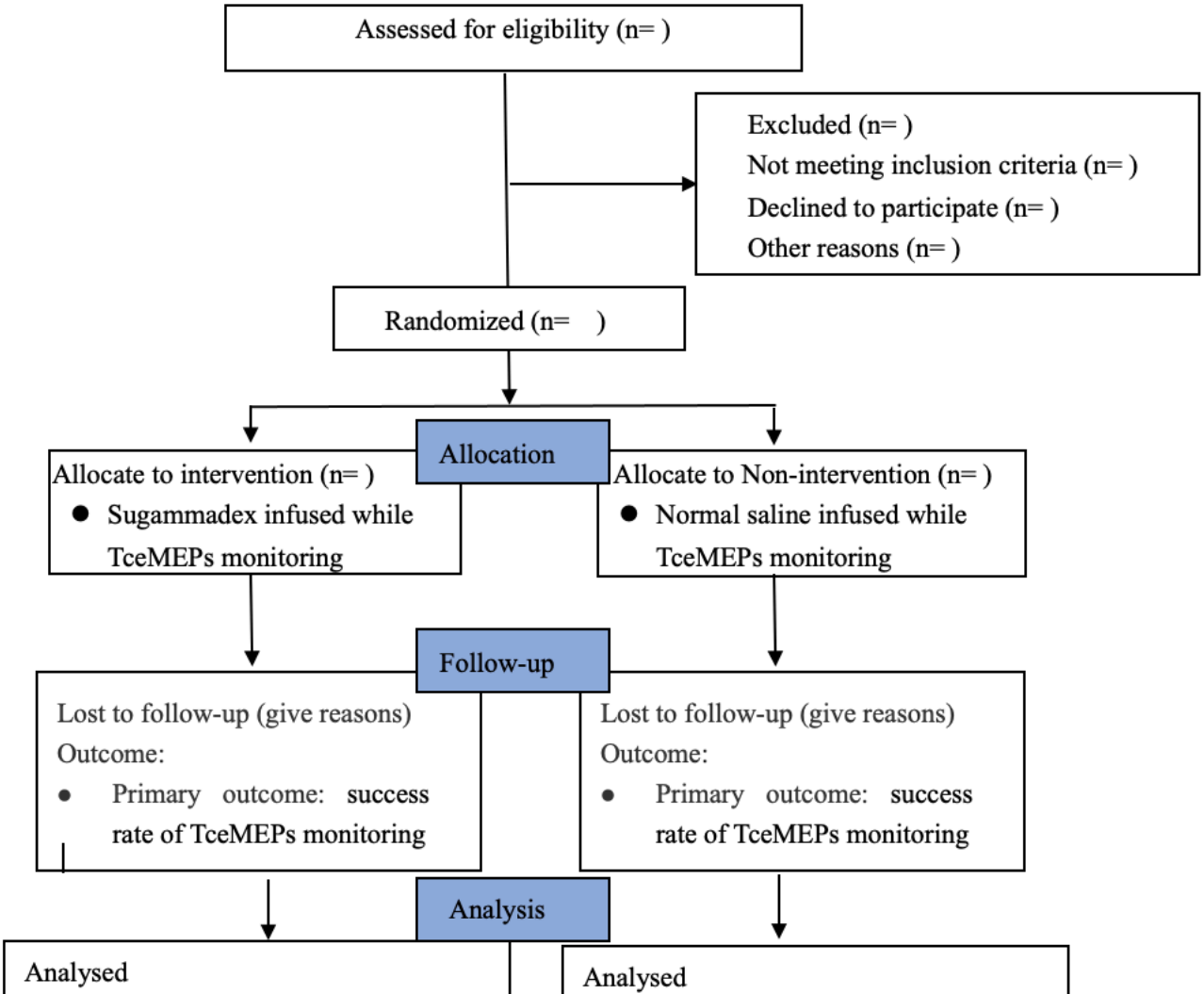
Assessed for eligibility (n=)
Excluded (n=)
Not meeting inclusion criteria (n=)
Declined to participate (n=)
Other reasons (n=)
Randomized (n=)
Allocation
Allocate to intervention (n=)
Sugammadex infused while TceMEPs monitoring
Allocate to Non-intervention (n=)
Normal saline infused while TceMEPs monitoring
Follow-up
Lost to follow-up (give reasons)
Outcome:
Primary outcome: success rate of TceMEPs monitoring
Lost to follow-up (give reasons)
Outcome:
Primary outcome: success rate of TceMEPs monitoring
Analysis
Analysed
Excluded from analysis (give reasons)
Analysed
Excluded from analysis (give reasons)

INFORMED CONSENT

Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential recording in Patients Undergoing Spinal Surgery

Project entrust organization: Beijing Tiantan Hospital

Contract Research Organization: N/A

Version : 2.0

2nd, June, 2021

INFORMATION SHEET

You will receive ***thoracic or lumbar spinal surgery***. We would like to invite you to participate our study, which is ***" Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential recording in Patients Undergoing Spinal Surgery"***, to evaluate the success rate of intraoperative muscle relax reversal by sugammadex on intraoperative TceMEP recording. This study is approved by Ethics Committee of Beijing Tiantan Hospital of Capital Medical University.During our study, we will follow the Declaration of Helsinki.

Before you decide whether participate this clinical trial, please take time to review this information carefully. This form describes the purpose, procedure, study duration, risks, and possible benefits of participating the study. You may also wish to talk to others, including your friends, family, or discuss with your anesthesiologist about your participation in this study.

1. PURPOSE of THIS STUDY

Intraoperative neuromonitoring (IOM) uses a combination of motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPs) to test neural integrity during spinal surgery. This method is reliable and validated for assessing spinal cord function. The Transcranial motor evoked potentials monitoring (TceMEPs) signals are exquisitely sensitive to neuromuscular blockade (NMB), the use of NMB is avoided except during intubation. However, appropriate muscle relaxation optimizes anaesthetic management, facilitates surgery, and prevents patient movement. Sugammadex is a modified γ-cyclodextrin derivative that selectively binds to NMB (rocuronium and vecuronium), which can reverse the rocuronium-induced neuromuscular blockade at the neuromuscular junction. The efficacy of reversing various levels of rocuronium block has been confirmed by multiple studies. Therefore, this study is a trial to compare the success rate of TceMEPs recording under partial NMB and no NMB reversed by sugammadex in spinal surgery.

2. NUMBER of PARTICIPANTS

In total, 162 patients will be included in the study.

3. WHO WILL PARTICIPANT IN THIS STUDY

- Age range from 18 to 65 years old
- American Society of Anaesthesiologists (ASA) physical status I to II

4. WHO SHOULD NOT PARTICIPATE in the STUDY

If you have following condition, you should not participate in the study:

- BMI ≥35 kg/m-2
- 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 <110 g/L
- TceMEPs stimulation or recorded site infection

- Preoperative neurological dysfunction in both upper extremities
- Cardiac pacemaker
- Pregnancy and lactation
- Any other investigational drugs used within 30 days of randomization or participated in another clinical trial within 30 days.

5. DURATION OF THIS STURY

This study will only be conducted during your hospital stay. You will be followed up at 2h, 24h, 48h, 72h after surgery for any adverse reactions, and your motor function will be assessed.

You can opt out of the research at any time without losing any benefits you should have received. However, if you decide to withdraw from this study during the study, we encourage you to consult with your doctor first. Considering your security issues, there may be a related check after you log out.

6. PROCESS OF THIS STUDY

If you are willing to participate in this study, your doctor will learn about your medical history, ask about your current disease, and current treatment medications to further confirm whether you are suitable for participating in this study.

If you are willing to participate in this study, during the general anesthesia of the operation, you have a half chance of using the closed-loop muscle relaxant injection system to maintain a moderate partial muscle relaxant and discontinue the muscle relaxants at the beginning of the key steps of the operation. There is also a one-half possibility of using a closed-loop muscle relaxant injection system to maintain a moderate partial muscle relaxant. At the beginning of the key steps of the operation, the muscle relaxant is discontinued, and the specific muscle relaxant antagonist is used at the same time. Later, the neurophysiologists will monitor your motor function to determine whether the operation will damage your motor function.

The day before your scheduled surgery, the researcher will determine whether you meet the inclusion-exclusion criteria of this study based on your disease and current status. If you agree to participate in the research, we will interview your medical details. After 2h, 24h, 48h, 72h, the researcher will examine your condition again. All visits will not cause you any harm. Participation in this study does not require changes to your surgical methods and postoperative treatment. Except for randomly entering a study group and receiving different administration methods of muscle relaxants, other anaesthesia management will not be affected in any way. Both medication regimens are safe. If you enter any research group, we will try your best to ensure that your surgery goes smoothly.

7. POSSIBLE BENEFITS of PARTICIPATING in the STUDY

The depth of anaesthesia and the degree of muscle relaxation will be under our strict monitoring to ensure the appropriate depth of anaesthesia and the success rate and accuracy of monitoring of TceMEPs during the operation. In addition, we will use the muscle relaxant antagonist Sugammadex free of charge for all subjects who use muscle relaxants after the operation, which will significantly reduce the occurrence of postoperative muscle relaxation and reduce complications related to muscle relaxation. The results obtained from this study may guide the use and management of intraoperative muscle relaxants in the future and bring benefits to patients undergoing similar operations.

8. POSSIBLE ADVERSE REACTIONS, RISKS and DISCOMFORT, INCONVENIENCES of PARTICIPATING in the STUDY

The adverse reactions of Sugammadex include nausea and vomiting, hypertension, and tachycardia. In this study, the dosage of Sugammadex is small and will not cause obvious adverse reactions. We have also formulated a detailed response plan if nausea and vomiting occur after surgery, you will be given antiemetic drugs; hypertension and tachycardia can be relieved by giving antihypertensive drugs.

If antagonistic drugs are not used during surgery, there may be a risk of failure in motor evoked potential monitoring. For this situation we have formulated the following remedy measures: ① Notify the surgeon and adjust the operation manipulation that may cause the failure of TceMEPs monitoring; ② Monitor the degree of muscle relaxation, and give appropriate amount of Sugammadex to maintain TOFr≥90%③Correct TceMEPs monitoring technical parameters, such as stimulation intensity, stimulation interval time and number of stimulation strings, etc.; ④ Correct Physiological parameter abnormalities that may occur during the operation, such as blood pressure, hemoglobin concentration, body temperature, arterial carbon dioxide partial pressure and body position, etc.; ⑤Adjust the depth of anesthesia under the guidance of the BIS value, and ensure that the BIS is ≤50 to avoid intraoperative awareness. The above plan will ensure your safety and the smooth progress of the operation.

If your health does suffer from research-related damage due to participation in this research, please notify the doctor immediately, who will be responsible for taking appropriate treatment measures for you. The sponsor, Beijing Tiatan Hospital, will bear the cost of treatment and provide you with corresponding financial compensation in accordance with relevant national regulations.Even if you have signed this informed consent form, you still retain all your legal rights.

9. OTHER TREATMENT CHOICE

If you do not participate in this study, you can choose your anesthesia treatment according to your anesthesiologist's suggestion.

10. YOU MAY VOLUNTARILY CHOOSE TO PARTICIPATE in the STUDY and WITHDRAW from the STUDY

Whether to participate in the study is entirely up to you. You may refuse to participate in the study or withdraw from the study at any time during the study, which will not affect your relationship with your doctor or affect your medical service or other benefits.

Before making decision, you can discuss with your family or friend， or you can talk with your doctor for any question, until you fully understand this study.

11. RELATED EXPENSES

Anesthetic drugs and surgical procedures are not free of charge. If you combine the treatment and examination required for other diseases, and if the treatment fails, the cost of changing to other treatment is not free of charge. If any medical expense happened due to adverse event, you will be exempted from the charge.

12. CONFIDENTIALITY of PERSONAL INFORMATION

Your medical records (study records /CRF, lab sheets, etc.) will be kept intact at the hospital. Your doctor will record the results of tests and other tests on your medical record. Researchers, ethics committees, and drug regulators will be allowed access to your medical records. Any public reports on the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical data within the law.

13. HOW TO GET MORE INFORMATION?

You can ask any questions about this study at any time and get answers. Your anesthesiologist will be ready to answer any of your questions before, during and after the study.

14. HOW THE STUDY MAY EFFECT YOUR LIFE?

You may feel the visit and examination uncomfortable and special arrangement is needed. You can consult your doctor in any steps of the study.

15. CONSULTING

If you have any related questions, please contact Dr. Jian Minyu (phone: 010-59976656 or cell phone: 13522550438).

If you have any concerns about your personal benefits, or you want to complain or express your concerns about the study, please contact the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (phone：010-59975178, email: ttyyirb@163.com).

SINGATURE PAGE OF AGREEMENT

Study title: Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential recording in Patients Undergoing Spinal Surgery

Principal Investigator: Ruquan Han, Beijing Tiantan Hospital, CMU

DECLARATION of CONSENT

I have read the introduction about the study above and have the opportunity to discuss with doctors and ask the questions about the study. All my questions have been answered satisfactorily.

I am aware of the possible risk and benefits of participating in this study. I know that participating in the study is voluntary. I have taken it into full consideration, and known that:

- I can ask my doctor for more information at any time.
- I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

I am also aware that if I withdraw from the study, especially if I withdraw due to medication, it will be of great benefit to the whole study if I tell my doctor about my condition and complete the corresponding physical examination and physical and chemical inspection.

If I need to take any other medication due to a change in my condition, I will consult my doctor beforehand or tell him afterwards truthfully.

I agree that the ethics committee of the drug regulatory authority or the representative of the sponsor may have access to my research information.

I will be provided with a signed and dated copy of the informed consent.

In the end, I agreed to participate in the study and promised to follow my doctors' advice as much as possible.

Signature of patient/legal relative:_____

Relation: _____

Date: _____ **(yyyy/mm/dd)**

I confirm that I have explained the details of the trial to the patients, including its rights and possible benefits and risks, and have given them a signed copy of the informed consent.

Signature of doctor:_____

Date: _____ **(yyyy/mm/dd)**

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2/17
	2b	All items from the World Health Organization Trial Registration Data Set	2/17
Protocol version	3	Date and version identifier	/
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	11
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____/_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____3-4_____
	6b	Explanation for choice of comparators	_____3-4_____
Objectives	7	Specific objectives or hypotheses	_____4_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____5_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____5_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	____5_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____5-6____

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____7___
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____/____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____7_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____7-8_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____/_____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____8_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____/_____

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5-6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5-7

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____ 8____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____8-9____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____8-9____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____8-9____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____/_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____/_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____9____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____/_____

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	/
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	/
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	/
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9

	31b	Authorship eligibility guidelines and any intended use of professional writers	_____/_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____9_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____/_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____/_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential Recording in Patients Undergoing Spinal Surgery: Study Protocol for a Randomized Controlled Trial

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Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential recording in Patients Undergoing Spinal Surgery: Study Protocol for a Randomized Controlled Trial

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Abstract:

Introduction: Transcranial motor evoked potentials (TceMEPs) 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 neuromuscular blockade. This study aims to evaluate the success rate of intraoperative muscle relax reversal by sugammadex on intraoperative TceMEP recording.

Methods and analysis: We will conduct a single centre randomized 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 to 1. Total intravenous anaesthesia by propofol and remifentanil will be performed in both groups. In the sugammadex group, patients will receive continuous infusion of rocuronium to produce a blockade maintained for at least two twitches in Train-of-four (TOF), rocuronium infusion will be discontinued and 2 mg/kg sugammadex will be given while performing TceMEPs monitoring. In the control group, rocuronium infusion will be discontinued and the same volume of saline will be infused while performing TceMEPs monitoring. The primary aim of this study is to evaluate the success rate of TceMEPs 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, July 16, 2021 (KY2021-082-02). The study was registered on clincaltrials.gov on Oct 25, 2020 (NCT04608682). Our study might guide neuromuscular blockade plans in TceMEPs 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: ClinicalTrials.gov Identifier: NCT04608682.

Keywords: Sugammadex, Motor Evoked Potentials, Spinal Surgery; Neuromuscular Blockade; Success Rate

Strengths and limitations of this study

- This study is a randomized controlled trial to evaluate the success rate of intraoperative muscle relaxation reversal by sugammadex on intraoperative transcranial motor evoked potentials recording under partial NMB or no NMB
- This study has a strict randomized system, clear inclusion and exclusion criteria and a rigorous uniform protocol to manage hemodynamic and respiratory parameters and depth of anaesthesia in both groups
- The abdductor pollicis brevis muscles are chosen to check the TceMEPs recording results, this may limit the generalization of our data to other muscle groups especially from lower limb muscles

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 (TceMEPs), 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].

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[3]. 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[4], which consists of total intravenous anaesthesia using propofol and remifentanil without the use of NMB.

However, appropriate muscle relaxation optimizes 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[5]. 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)[6]. Kalkman maintained pNMB at T1 twitch height of 5–15%, whereas additional classification of pNMB aimed at T1 twitch height of 45–55% by van Dongen led to contrasting results[7 8]. Liu et al has 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 TIVA. Nevertheless, the incidence of monitoring failure and false-positive results was increased under pNMB[5 9].

Sugammadex is a modified γ-cyclodextrin derivative that selectively binds to NMB (rocuronium and vecuronium), which can encapsulate rocuronium and reverse the rocuronium-induced neuromuscular blockade at the neuromuscular junction[10]. 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) [11-14]. With these doses, it takes 2-3 minutes 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 [15].

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 randomized controlled trial to compare the success rate of TceMEPs recording under partial NMB and no NMB reversed by sugammadex. We hypothesize 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, randomized 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 at ClinicalTrials.gov (NCT04608682) on October 25, 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 ≥35 kg/m^2; 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 <110 g/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 randomization or have participated in another clinical trial within 30 days.

Randomization and blinding

Written informed consent will be obtained during preoperative evaluation by an anaesthesiologist. See Supplementary file 1 for the patient informed consent. Subsequently, each patient will be randomly allocated to either the sugammadex group or control group. Randomization will be performed by a computer-generated table. The allocation plan will be conducted using a variable block randomization 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 randomization 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 Technology Co., Ltd, China.). The electrodes will be positioned near the ulnar nerve. The acceleromyograph transducer (CLMRIS-I，Guangxi VERYARK Technology Co., Ltd, 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 5 s and 50 Hz tetanic stimulation of ulnar nerve after administration of propofol prior to muscle relaxation. Subsequently, repetitive TOF stimulation will be conducted every 15 s. 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 0.6 ug/kg/min and subsequently adjusted up to 12 ug/kg/min, and the bolus rate is 30 ug/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, past medical history, diagnosis, type of surgery, preoperative motor function assessment and ASA physical status.

Standard ASA parameters will be monitored perioperatively, including blood pressure, electrocardiogram, pulse oxygen saturation, body temperature, and end-tidal carbon dioxide partial pressure ($ETCO_2$). 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 6 μg/mL and a remifentanil target concentration of 4 ng/mL will be set to allow intubation. Additionally, 0.6 mg/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 $PaCO_2$

at 35 to 40 mmHg. 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 to 6 ug/mL to maintain a BIS (BIS Vista monitor, Aspect Medical Systems, Natick, MA) value of 40 to 50. The mean arterial pressure (MAP) and heart rate (HR) will be maintained at a level of ± 20% compared to 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 and 37℃ using an insulation blanket.

Acquisition of TceMEPs

The acquisition of TceMEPs has been described previously[4]. Patients in both groups will be monitored with TceMEPs (Nicolet Neurological Workstation, Endeavor 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 0.3 ms, with five pulses and an interstimulus interval of 2 ms. The maximum stimulation intensity will be 200V. The filter range is 300 to 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 uV are obtained. These voltage levels are considered as TceMEPs threshold intensities for monitoring in surgery. The neurophysiologists will collect TceMEPs waveforms twice under the same stimulation threshold, if both of waveforms are more than 50uv, which will be defined as “repeatable” waveform. The success of TceMEPs is defined as collecting repeatable and stable TceMEPs waveforms (wave amplitude ≥ 50uv) 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 minutes after first performing of TceMEPs.

See Figure 1 for a flow diagram of the study.

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)[16]. 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[17]. 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 TOFr>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 minutes 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 minutes 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 minutes 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 (heart rate lower than 60bpm), postprocedural pain, nausea and vomiting, fever (body temperature more than 37.3℃), and diarrhea, etc[18].
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 neuromuscular blockade defined as TOFr < 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 15 software (NCSS, LLC, USA) is used to calculate the sample size based on the primary endpoint. According to a previous study[6], the success rate of TceMEPs is about 80% under pNMB, we hypothesize 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 eighty-one 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 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 summarized by percentage and number of patients.

The mean value of amplitudes of TceMEPs in the abductor pollicis brevis muscles of both upper extremities 5 minutes 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 ANOVA 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 chi-square 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 stabilization 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 July 16, 2021 (KY2021-082-02). The study was registered on clincaltrials.gov on October 25, 2020 (NCT04608682). The study recruited the first patient on August 16, 2021, and the estimated study completion date will be December 30, 2022. The findings of the study will be published in peer-reviewed journals and will be presented at national or international conferences.

See Supplementary file 2 for the SPIRIT checklist.

Discussion

The purpose of TceMEPs 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 randomized controlled trial to evaluate the success rate of TceMEPs monitoring in patients undergoing spinal surgery on intraoperative reversal of muscle relaxant. The interpretation of TceMEPs can be affected by multiple factors such as hypothermia, hypotension, hypoxemia, electrolyte imbalance and depth of anaesthesia[19]. These factors will be tightly controlled in our study.

NMB abolishes myogenic motor-evoked potentials and increases the risk of neurological injury when performing TceMEPs. Therefore, muscle relaxants should be omitted during TceMEPs 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 TceMEPs 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[5]. Moreover, high peak insufflation pressure could occur without NMB.

Under these circumstances, pNMB seems to be preferable to the surgical team. However, the partially paralyzed 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 ischemia. 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 TceMEPs monitoring.

Theoretically, the availability of sugammadex makes it possible to use NMB during spinal surgery to improve surgical conditions without affecting TceMEPs 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 our knowledge, there is no data on whether the sugammadex molecule itself has any interference on TceMEPs. Pavoni and Batistaki et al[14,22] 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 TceMEPs signals, i.e., 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 limitation, 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 TceMEPs recording results. This may limit the generalization 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 TceMEPs.

In summary, this parallel group, randomized, controlled trial aims to assess whether use of sugammadex is effective and safe for reversal of muscle relaxants during TceMEPs monitoring in spinal surgery. The features of the current study involve a strict randomized system, clear inclusion and exclusion criteria and a rigorous uniform protocol to manage hemodynamic 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 TceMEPs monitoring during spinal surgery.

Ethics approval and consent to participate

The trial has been approved by the Institutional Review Board of Beijing Tiantan Hospital on July 16, 2021 (KY2021-082-02). Written informed consent will be obtained from all participants.

Patient and Public Involvement

Patients and the public were not involved in the trial design. Participants will have access to the findings of the study on request.

Consent for publication

Written informed consent for publication will be obtained from all participants.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors have no potential conflicts of interest to declare with respect to the research, authorship, and/or publication of this article.

Funding

This study was supported by funding from Clinical Medicine Development of Special Funding Support from the Beijing Municipal Administration of Hospitals (ZYLX201708; DFL20180502), and WUJIEPING medical foundation (320.6750.18176, 320.6750.2021-05-1).

Author contributions

RH and HL conceived the primary idea of the study. All authors contributed to the writing of the protocol. BM, 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.

List of tables and figures

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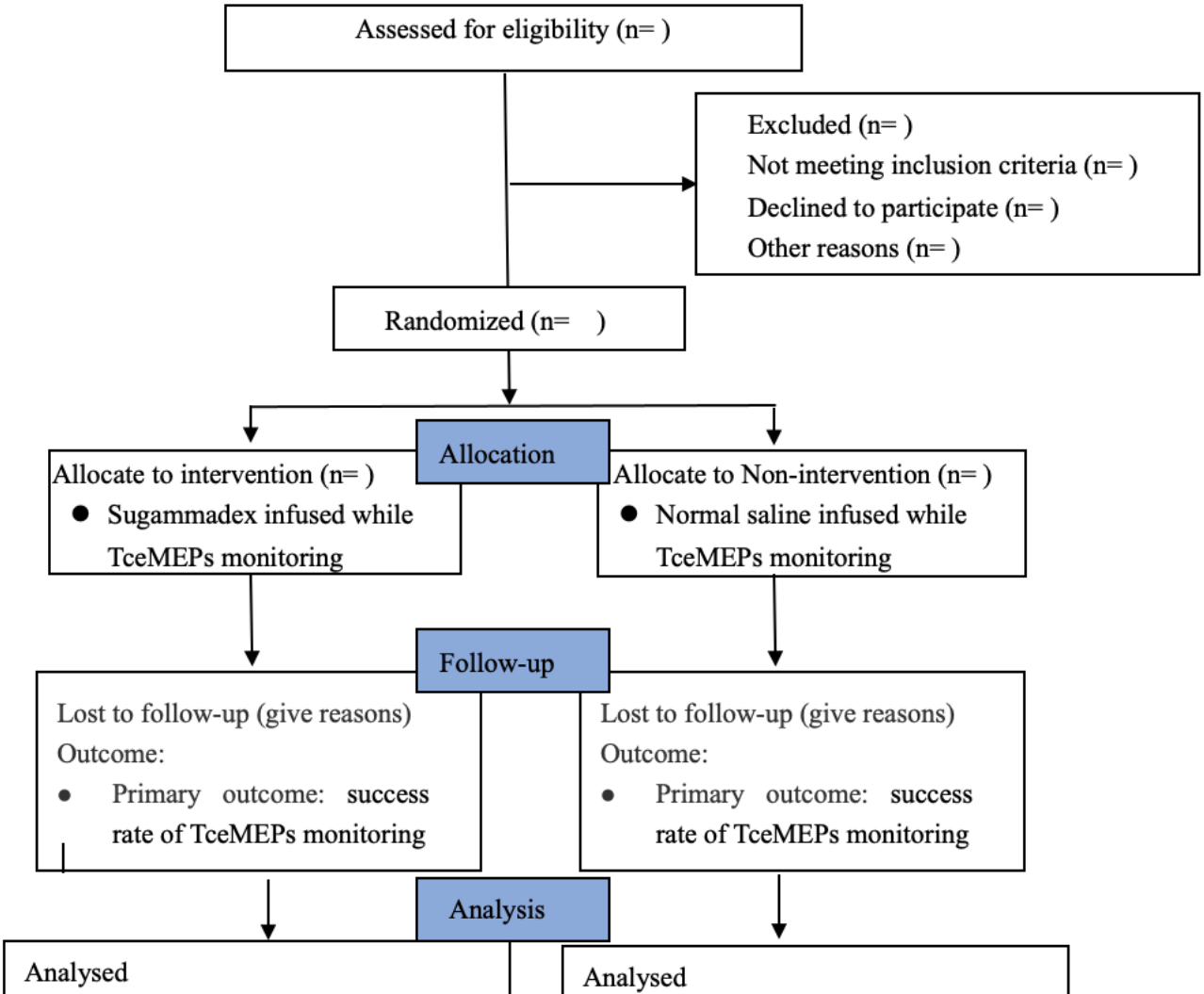
Assessed for eligibility (n=)
Excluded (n=)
Not meeting inclusion criteria (n=)
Declined to participate (n=)
Other reasons (n=)
Randomized (n=)
Allocation
Allocate to intervention (n=)
Sugammadex infused while TceMEPs monitoring
Allocate to Non-intervention (n=)
Normal saline infused while TceMEPs monitoring
Follow-up
Lost to follow-up (give reasons)
Outcome:
Primary outcome: success rate of TceMEPs monitoring
Lost to follow-up (give reasons)
Outcome:
Primary outcome: success rate of TceMEPs monitoring
Analysis
Analysed
Excluded from analysis (give reasons)
Analysed
Excluded from analysis (give reasons)

INFORMED CONSENT

Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential recording in Patients Undergoing Spinal Surgery

Project entrust organization: Beijing Tiantan Hospital

Contract Research Organization: N/A

Version : 2.0

2nd, June, 2021

INFORMATION SHEET

You will receive ***thoracic or lumbar spinal surgery***. We would like to invite you to participate our study, which is ***" Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential recording in Patients Undergoing Spinal Surgery"***, to evaluate the success rate of intraoperative muscle relax reversal by sugammadex on intraoperative TceMEP recording. This study is approved by Ethics Committee of Beijing Tiantan Hospital of Capital Medical University.During our study, we will follow the Declaration of Helsinki.

Before you decide whether participate this clinical trial, please take time to review this information carefully. This form describes the purpose, procedure, study duration, risks, and possible benefits of participating the study. You may also wish to talk to others, including your friends, family, or discuss with your anesthesiologist about your participation in this study.

1. PURPOSE of THIS STUDY

Intraoperative neuromonitoring (IOM) uses a combination of motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPs) to test neural integrity during spinal surgery. This method is reliable and validated for assessing spinal cord function. The Transcranial motor evoked potentials monitoring (TceMEPs) signals are exquisitely sensitive to neuromuscular blockade (NMB), the use of NMB is avoided except during intubation. However, appropriate muscle relaxation optimizes anaesthetic management, facilitates surgery, and prevents patient movement. Sugammadex is a modified γ-cyclodextrin derivative that selectively binds to NMB (rocuronium and vecuronium), which can reverse the rocuronium-induced neuromuscular blockade at the neuromuscular junction. The efficacy of reversing various levels of rocuronium block has been confirmed by multiple studies. Therefore, this study is a trial to compare the success rate of TceMEPs recording under partial NMB and no NMB reversed by sugammadex in spinal surgery.

2. NUMBER of PARTICIPANTS

In total, 162 patients will be included in the study.

3. WHO WILL PARTICIPANT IN THIS STUDY

- Age range from 18 to 65 years old
- American Society of Anaesthesiologists (ASA) physical status I to II

4. WHO SHOULD NOT PARTICIPATE in the STUDY

If you have following condition, you should not participate in the study:

- BMI ≥35 kg/m-2
- 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 <110 g/L
- TceMEPs stimulation or recorded site infection

- Preoperative neurological dysfunction in both upper extremities
- Cardiac pacemaker
- Pregnancy and lactation
- Any other investigational drugs used within 30 days of randomization or participated in another clinical trial within 30 days.

5. DURATION OF THIS STURY

This study will only be conducted during your hospital stay. You will be followed up at 2h, 24h, 48h, 72h after surgery for any adverse reactions, and your motor function will be assessed.

You can opt out of the research at any time without losing any benefits you should have received. However, if you decide to withdraw from this study during the study, we encourage you to consult with your doctor first. Considering your security issues, there may be a related check after you log out.

6. PROCESS OF THIS STUDY

If you are willing to participate in this study, your doctor will learn about your medical history, ask about your current disease, and current treatment medications to further confirm whether you are suitable for participating in this study.

If you are willing to participate in this study, during the general anesthesia of the operation, you have a half chance of using the closed-loop muscle relaxant injection system to maintain a moderate partial muscle relaxant and discontinue the muscle relaxants at the beginning of the key steps of the operation. There is also a one-half possibility of using a closed-loop muscle relaxant injection system to maintain a moderate partial muscle relaxant. At the beginning of the key steps of the operation, the muscle relaxant is discontinued, and the specific muscle relaxant antagonist is used at the same time. Later, the neurophysiologists will monitor your motor function to determine whether the operation will damage your motor function.

The day before your scheduled surgery, the researcher will determine whether you meet the inclusion-exclusion criteria of this study based on your disease and current status. If you agree to participate in the research, we will interview your medical details. After 2h, 24h, 48h, 72h, the researcher will examine your condition again. All visits will not cause you any harm. Participation in this study does not require changes to your surgical methods and postoperative treatment. Except for randomly entering a study group and receiving different administration methods of muscle relaxants, other anaesthesia management will not be affected in any way. Both medication regimens are safe. If you enter any research group, we will try your best to ensure that your surgery goes smoothly.

7. POSSIBLE BENEFITS of PARTICIPATING in the STUDY

The depth of anaesthesia and the degree of muscle relaxation will be under our strict monitoring to ensure the appropriate depth of anaesthesia and the success rate and accuracy of monitoring of TceMEPs during the operation. In addition, we will use the muscle relaxant antagonist Sugammadex free of charge for all subjects who use muscle relaxants after the operation, which will significantly reduce the occurrence of postoperative muscle relaxation and reduce complications related to muscle relaxation. The results obtained from this study may guide the use and management of intraoperative muscle relaxants in the future and bring benefits to patients undergoing similar operations.

8. POSSIBLE ADVERSE REACTIONS, RISKS and DISCOMFORT, INCONVENIENCES of PARTICIPATING in the STUDY

The adverse reactions of Sugammadex include nausea and vomiting, hypertension, and tachycardia. In this study, the dosage of Sugammadex is small and will not cause obvious adverse reactions. We have also formulated a detailed response plan if nausea and vomiting occur after surgery, you will be given antiemetic drugs; hypertension and tachycardia can be relieved by giving antihypertensive drugs.

If antagonistic drugs are not used during surgery, there may be a risk of failure in motor evoked potential monitoring. For this situation we have formulated the following remedy measures: ① Notify the surgeon and adjust the operation manipulation that may cause the failure of TceMEPs monitoring; ② Monitor the degree of muscle relaxation, and give appropriate amount of Sugammadex to maintain TOFr≥90%③Correct TceMEPs monitoring technical parameters, such as stimulation intensity, stimulation interval time and number of stimulation strings, etc.; ④ Correct Physiological parameter abnormalities that may occur during the operation, such as blood pressure, hemoglobin concentration, body temperature, arterial carbon dioxide partial pressure and body position, etc.; ⑤Adjust the depth of anesthesia under the guidance of the BIS value, and ensure that the BIS is ≤50 to avoid intraoperative awareness. The above plan will ensure your safety and the smooth progress of the operation.

If your health does suffer from research-related damage due to participation in this research, please notify the doctor immediately, who will be responsible for taking appropriate treatment measures for you. The sponsor, Beijing Tiatan Hospital, will bear the cost of treatment and provide you with corresponding financial compensation in accordance with relevant national regulations.Even if you have signed this informed consent form, you still retain all your legal rights.

9. OTHER TREATMENT CHOICE

If you do not participate in this study, you can choose your anesthesia treatment according to your anesthesiologist's suggestion.

10. YOU MAY VOLUNTARILY CHOOSE TO PARTICIPATE in the STUDY and WITHDRAW from the STUDY

Whether to participate in the study is entirely up to you. You may refuse to participate in the study or withdraw from the study at any time during the study, which will not affect your relationship with your doctor or affect your medical service or other benefits.

Before making decision, you can discuss with your family or friend， or you can talk with your doctor for any question, until you fully understand this study.

11. RELATED EXPENSES

Anesthetic drugs and surgical procedures are not free of charge. If you combine the treatment and examination required for other diseases, and if the treatment fails, the cost of changing to other treatment is not free of charge. If any medical expense happened due to adverse event, you will be exempted from the charge.

12. CONFIDENTIALITY of PERSONAL INFORMATION

Your medical records (study records /CRF, lab sheets, etc.) will be kept intact at the hospital. Your doctor will record the results of tests and other tests on your medical record. Researchers, ethics committees, and drug regulators will be allowed access to your medical records. Any public reports on the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical data within the law.

13. HOW TO GET MORE INFORMATION?

You can ask any questions about this study at any time and get answers. Your anesthesiologist will be ready to answer any of your questions before, during and after the study.

14. HOW THE STUDY MAY EFFECT YOUR LIFE?

You may feel the visit and examination uncomfortable and special arrangement is needed. You can consult your doctor in any steps of the study.

15. CONSULTING

If you have any related questions, please contact Dr. Jian Minyu (phone: 010-59976656 or cell phone: 13522550438).

If you have any concerns about your personal benefits, or you want to complain or express your concerns about the study, please contact the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (phone：010-59975178, email: ttyyirb@163.com).

SINGATURE PAGE OF AGREEMENT

Study title: Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential recording in Patients Undergoing Spinal Surgery

Principal Investigator: Ruquan Han, Beijing Tiantan Hospital, CMU

DECLARATION of CONSENT

I have read the introduction about the study above and have the opportunity to discuss with doctors and ask the questions about the study. All my questions have been answered satisfactorily.

I am aware of the possible risk and benefits of participating in this study. I know that participating in the study is voluntary. I have taken it into full consideration, and known that:

- I can ask my doctor for more information at any time.
- I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

I am also aware that if I withdraw from the study, especially if I withdraw due to medication, it will be of great benefit to the whole study if I tell my doctor about my condition and complete the corresponding physical examination and physical and chemical inspection.

If I need to take any other medication due to a change in my condition, I will consult my doctor beforehand or tell him afterwards truthfully.

I agree that the ethics committee of the drug regulatory authority or the representative of the sponsor may have access to my research information.

I will be provided with a signed and dated copy of the informed consent.

In the end, I agreed to participate in the study and promised to follow my doctors' advice as much as possible.

Signature of patient/legal relative:_____

Relation: _____

Date: _____ **(yyyy/mm/dd)**

I confirm that I have explained the details of the trial to the patients, including its rights and possible benefits and risks, and have given them a signed copy of the informed consent.

Signature of doctor:_____

Date: _____ **(yyyy/mm/dd)**

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2/17
	2b	All items from the World Health Organization Trial Registration Data Set	2/17
Protocol version	3	Date and version identifier	/
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	11
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____/_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____3-4_____
	6b	Explanation for choice of comparators	_____3-4_____
Objectives	7	Specific objectives or hypotheses	_____4_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____5_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____5_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	____5_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____5-6____

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____7___
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____/____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____7_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____7-8_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____/_____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____8_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____/_____

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5-6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5-7

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____ 8____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____8-9____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____8-9____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____8-9____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____/_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____/_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____9____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____/_____

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	/
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	/
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	/
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9

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Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____/_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____/_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential Recording in Patients Undergoing Spinal Surgery: Study Protocol for a Randomized Controlled Trial

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Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential recording in Patients Undergoing Spinal Surgery: Study Protocol for a Randomized Controlled Trial

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Abstract:

Introduction: Transcranial motor evoked potentials (TceMEPs) 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 neuromuscular blockade. This study aims to evaluate the success rate of intraoperative muscle relax reversal by sugammadex on intraoperative TceMEP recording.

Methods and analysis: We will conduct a single centre randomized 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 to 1. Total intravenous anaesthesia by propofol and remifentanil will be performed in both groups. In the sugammadex group, patients will receive continuous infusion of rocuronium to produce a blockade maintained for at least two twitches in Train-of-four (TOF), rocuronium infusion will be discontinued and 2 mg/kg sugammadex will be given while performing TceMEPs monitoring. In the control group, rocuronium infusion will be discontinued and the same volume of saline will be infused while performing TceMEPs monitoring. The primary aim of this study is to evaluate the success rate of TceMEPs 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, July 16, 2021 (KY2021-082-02). The study was registered on clincaltrials.gov on Oct 25, 2020 (NCT04608682). Our study might guide neuromuscular blockade plans in TceMEPs 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: ClinicalTrials.gov Identifier: NCT04608682.

Keywords: Sugammadex, Motor Evoked Potentials, Spinal Surgery; Neuromuscular Blockade; Success Rate

Strengths and limitations of this study

- This study is a randomized controlled trial to evaluate the success rate of intraoperative muscle relaxation reversal by sugammadex on intraoperative transcranial motor evoked potentials recording under partial NMB or no NMB
- This study has a strict randomized system, clear inclusion and exclusion criteria and a rigorous uniform protocol to manage hemodynamic and respiratory parameters and depth of anaesthesia in both groups
- The abdductor pollicis brevis muscles are chosen to check the TceMEPs recording results, this may limit the generalization of our data to other muscle groups especially from lower limb muscles

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 (TceMEPs), 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].

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[3]. 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[4], which consists of total intravenous anaesthesia using propofol and remifentanil without the use of NMB.

However, appropriate muscle relaxation optimizes 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[5]. 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)[6]. Kalkman maintained pNMB at T1 twitch height of 5–15%, whereas additional classification of pNMB aimed at T1 twitch height of 45–55% by van Dongen led to contrasting results[7 8]. Liu et al has 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 TIVA. Nevertheless, the incidence of monitoring failure and false-positive results was increased under pNMB[5 9].

Sugammadex is a modified γ-cyclodextrin derivative that selectively binds to NMB (rocuronium and vecuronium), which can encapsulate rocuronium and reverse the rocuronium-induced neuromuscular blockade at the neuromuscular junction[10]. 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) [11-14]. With these doses, it takes 2-3 minutes 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 [15].

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 randomized controlled trial to compare the success rate of TceMEPs recording under partial NMB and no NMB reversed by sugammadex. We hypothesize 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, randomized 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 at ClinicalTrials.gov (NCT04608682) on October 25, 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 ≥35 kg/m^2; 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 <110 g/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 randomization or have participated in another clinical trial within 30 days.

Randomization and blinding

Written informed consent will be obtained during preoperative evaluation by an anaesthesiologist. See Supplementary file 1 for the patient informed consent. Subsequently, each patient will be randomly allocated to either the sugammadex group or control group. Randomization will be performed by a computer-generated table. The allocation plan will be conducted using a variable block randomization 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 randomization 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 Technology Co., Ltd, China.). The electrodes will be positioned near the ulnar nerve. The acceleromyograph transducer (CLMRIS-I，Guangxi VERYARK Technology Co., Ltd, 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 5 s and 50 Hz tetanic stimulation of ulnar nerve after administration of propofol prior to muscle relaxation. Subsequently, repetitive TOF stimulation will be conducted every 15 s. 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 0.6 ug/kg/min and subsequently adjusted up to 12 ug/kg/min, and the bolus rate is 30 ug/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, past medical history, diagnosis, type of surgery, preoperative motor function assessment and ASA physical status.

Standard ASA parameters will be monitored perioperatively, including blood pressure, electrocardiogram, pulse oxygen saturation, body temperature, and end-tidal carbon dioxide partial pressure ($ETCO_2$). 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 6 μg/mL and a remifentanil target concentration of 4 ng/mL will be set to allow intubation. Additionally, 0.6 mg/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 $PaCO_2$

at 35 to 40 mmHg. 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 to 6 ug/mL to maintain a BIS (BIS Vista monitor, Aspect Medical Systems, Natick, MA) value of 40 to 50. The mean arterial pressure (MAP) and heart rate (HR) will be maintained at a level of ± 20% compared to 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 and 37℃ using an insulation blanket.

Acquisition of TceMEPs

The acquisition of TceMEPs has been described previously[4]. Patients in both groups will be monitored with TceMEPs (Nicolet Neurological Workstation, Endeavor 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 0.3 ms, with five pulses and an interstimulus interval of 2 ms. The maximum stimulation intensity will be 200V. The filter range is 300 to 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 uV are obtained. These voltage levels are considered as TceMEPs threshold intensities for monitoring in surgery. The neurophysiologists will collect TceMEPs waveforms twice under the same stimulation threshold, if both of waveforms are more than 50uv, which will be defined as “repeatable” waveform. The success of TceMEPs is defined as collecting repeatable and stable TceMEPs waveforms (wave amplitude ≥ 50uv) 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 minutes after first performing of TceMEPs.

See Figure 1 for a flow diagram of the study.

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)[16]. 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[17]. 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 TOFr>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 minutes 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 minutes 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 minutes 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 (heart rate lower than 60bpm), postprocedural pain, nausea and vomiting, fever (body temperature more than 37.3℃), and diarrhea, etc[18].
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 neuromuscular blockade defined as TOFr < 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 15 software (NCSS, LLC, USA) is used to calculate the sample size based on the primary endpoint. According to a previous study[6], the success rate of TceMEPs is about 80% under pNMB, we hypothesize 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 eighty-one 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 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 summarized by percentage and number of patients.

The mean value of amplitudes of TceMEPs in the abductor pollicis brevis muscles of both upper extremities 5 minutes 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 ANOVA 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 chi-square 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 stabilization 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 July 16, 2021 (KY2021-082-02). The study was registered on clincaltrials.gov on October 25, 2020 (NCT04608682). The study recruited the first patient on August 16, 2021, and the estimated study completion date will be December 30, 2022. The findings of the study will be published in peer-reviewed journals and will be presented at national or international conferences.

See Supplementary file 2 for the SPIRIT checklist.

Discussion

The purpose of TceMEPs 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 randomized controlled trial to evaluate the success rate of TceMEPs monitoring in patients undergoing spinal surgery on intraoperative reversal of muscle relaxant. The interpretation of TceMEPs can be affected by multiple factors such as hypothermia, hypotension, hypoxemia, electrolyte imbalance and depth of anaesthesia[19]. These factors will be tightly controlled in our study.

NMB abolishes myogenic motor-evoked potentials and increases the risk of neurological injury when performing TceMEPs. Therefore, muscle relaxants should be omitted during TceMEPs 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 TceMEPs 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[5]. Moreover, high peak insufflation pressure could occur without NMB.

Under these circumstances, pNMB seems to be preferable to the surgical team. However, the partially paralyzed 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 ischemia. 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 TceMEPs monitoring.

Theoretically, the availability of sugammadex makes it possible to use NMB during spinal surgery to improve surgical conditions without affecting TceMEPs 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 our knowledge, there is no data on whether the sugammadex molecule itself has any interference on TceMEPs. Pavoni and Batistaki et al[14,22] 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 TceMEPs signals, i.e., 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 limitation, 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 TceMEPs recording results. This may limit the generalization 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 TceMEPs.

In summary, this parallel group, randomized, controlled trial aims to assess whether use of sugammadex is effective and safe for reversal of muscle relaxants during TceMEPs monitoring in spinal surgery. The features of the current study involve a strict randomized system, clear inclusion and exclusion criteria and a rigorous uniform protocol to manage hemodynamic 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 TceMEPs monitoring during spinal surgery.

Ethics approval and consent to participate

The trial has been approved by the Institutional Review Board of Beijing Tiantan Hospital on July 16, 2021 (KY2021-082-02). Written informed consent will be obtained from all participants.

Patient and Public Involvement

Patients and the public were not involved in the trial design. Participants will have access to the findings of the study on request.

Consent for publication

Written informed consent for publication will be obtained from all participants.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors have no potential conflicts of interest to declare with respect to the research, authorship, and/or publication of this article.

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Author contributions

RH and HL conceived the primary idea of the study. All authors contributed to the writing of the protocol. BM, 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.

List of tables and figures

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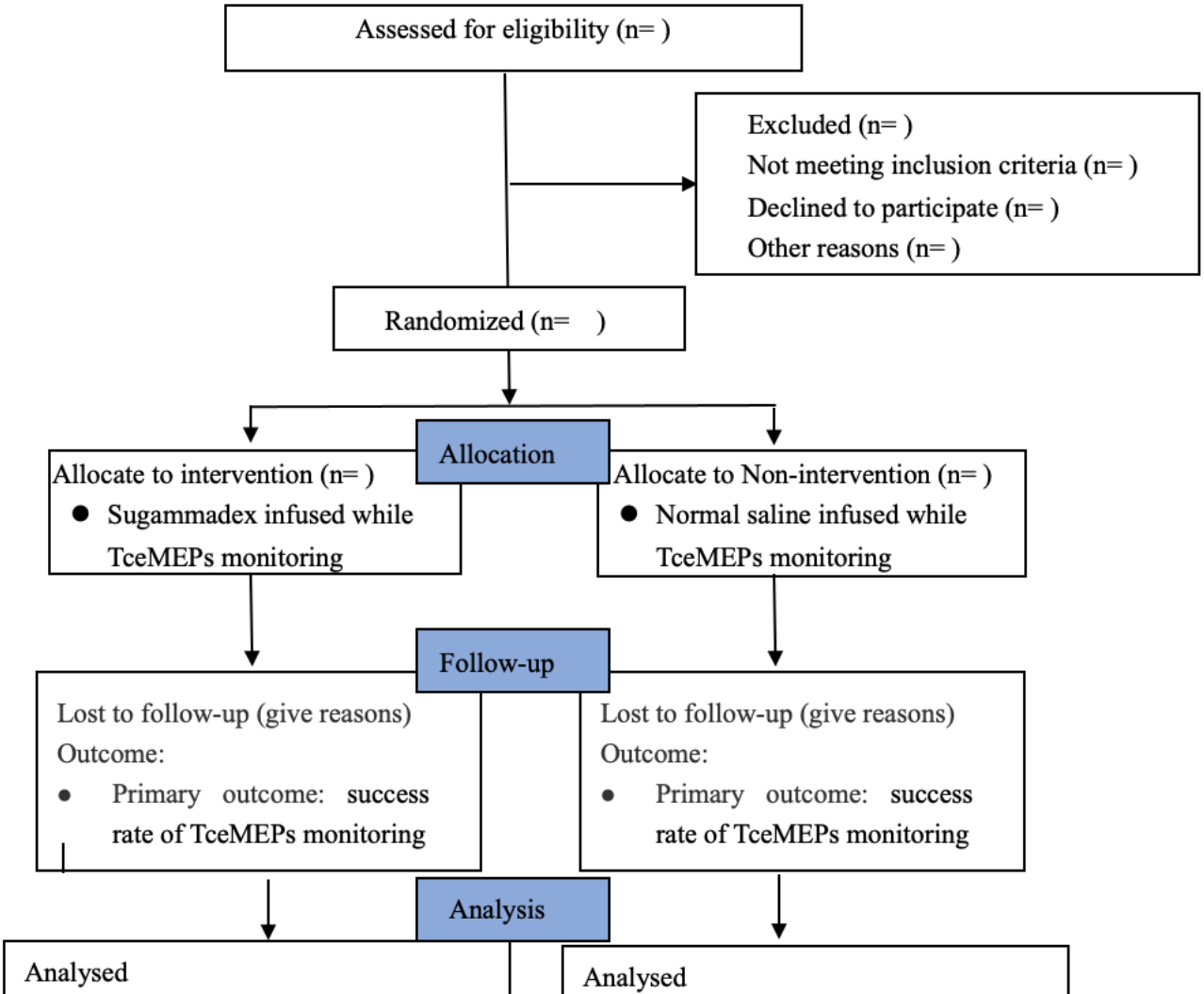
Assessed for eligibility (n=)
Excluded (n=)
Not meeting inclusion criteria (n=)
Declined to participate (n=)
Other reasons (n=)
Randomized (n=)
Allocation
Allocate to intervention (n=)
Sugammadex infused while TceMEPs monitoring
Allocate to Non-intervention (n=)
Normal saline infused while TceMEPs monitoring
Follow-up
Lost to follow-up (give reasons)
Outcome:
Primary outcome: success rate of TceMEPs monitoring
Lost to follow-up (give reasons)
Outcome:
Primary outcome: success rate of TceMEPs monitoring
Analysis
Analysed
Excluded from analysis (give reasons)
Analysed
Excluded from analysis (give reasons)

INFORMED CONSENT

Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential recording in Patients Undergoing Spinal Surgery

Project entrust organization: Beijing Tiantan Hospital

Contract Research Organization: N/A

Version : 2.0

2nd, June, 2021

INFORMATION SHEET

You will receive ***thoracic or lumbar spinal surgery***. We would like to invite you to participate our study, which is ***" Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential recording in Patients Undergoing Spinal Surgery"***, to evaluate the success rate of intraoperative muscle relax reversal by sugammadex on intraoperative TceMEP recording. This study is approved by Ethics Committee of Beijing Tiantan Hospital of Capital Medical University.During our study, we will follow the Declaration of Helsinki.

Before you decide whether participate this clinical trial, please take time to review this information carefully. This form describes the purpose, procedure, study duration, risks, and possible benefits of participating the study. You may also wish to talk to others, including your friends, family, or discuss with your anesthesiologist about your participation in this study.

1. PURPOSE of THIS STUDY

Intraoperative neuromonitoring (IOM) uses a combination of motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPs) to test neural integrity during spinal surgery. This method is reliable and validated for assessing spinal cord function. The Transcranial motor evoked potentials monitoring (TceMEPs) signals are exquisitely sensitive to neuromuscular blockade (NMB), the use of NMB is avoided except during intubation. However, appropriate muscle relaxation optimizes anaesthetic management, facilitates surgery, and prevents patient movement. Sugammadex is a modified γ-cyclodextrin derivative that selectively binds to NMB (rocuronium and vecuronium), which can reverse the rocuronium-induced neuromuscular blockade at the neuromuscular junction. The efficacy of reversing various levels of rocuronium block has been confirmed by multiple studies. Therefore, this study is a trial to compare the success rate of TceMEPs recording under partial NMB and no NMB reversed by sugammadex in spinal surgery.

2. NUMBER of PARTICIPANTS

In total, 162 patients will be included in the study.

3. WHO WILL PARTICIPANT IN THIS STUDY

- Age range from 18 to 65 years old
- American Society of Anaesthesiologists (ASA) physical status I to II

4. WHO SHOULD NOT PARTICIPATE in the STUDY

If you have following condition, you should not participate in the study:

- BMI ≥35 kg/m-2
- 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 <110 g/L
- TceMEPs stimulation or recorded site infection

- Preoperative neurological dysfunction in both upper extremities
- Cardiac pacemaker
- Pregnancy and lactation
- Any other investigational drugs used within 30 days of randomization or participated in another clinical trial within 30 days.

5. DURATION OF THIS STURY

This study will only be conducted during your hospital stay. You will be followed up at 2h, 24h, 48h, 72h after surgery for any adverse reactions, and your motor function will be assessed.

You can opt out of the research at any time without losing any benefits you should have received. However, if you decide to withdraw from this study during the study, we encourage you to consult with your doctor first. Considering your security issues, there may be a related check after you log out.

6. PROCESS OF THIS STUDY

If you are willing to participate in this study, your doctor will learn about your medical history, ask about your current disease, and current treatment medications to further confirm whether you are suitable for participating in this study.

If you are willing to participate in this study, during the general anesthesia of the operation, you have a half chance of using the closed-loop muscle relaxant injection system to maintain a moderate partial muscle relaxant and discontinue the muscle relaxants at the beginning of the key steps of the operation. There is also a one-half possibility of using a closed-loop muscle relaxant injection system to maintain a moderate partial muscle relaxant. At the beginning of the key steps of the operation, the muscle relaxant is discontinued, and the specific muscle relaxant antagonist is used at the same time. Later, the neurophysiologists will monitor your motor function to determine whether the operation will damage your motor function.

The day before your scheduled surgery, the researcher will determine whether you meet the inclusion-exclusion criteria of this study based on your disease and current status. If you agree to participate in the research, we will interview your medical details. After 2h, 24h, 48h, 72h, the researcher will examine your condition again. All visits will not cause you any harm. Participation in this study does not require changes to your surgical methods and postoperative treatment. Except for randomly entering a study group and receiving different administration methods of muscle relaxants, other anaesthesia management will not be affected in any way. Both medication regimens are safe. If you enter any research group, we will try your best to ensure that your surgery goes smoothly.

7. POSSIBLE BENEFITS of PARTICIPATING in the STUDY

The depth of anaesthesia and the degree of muscle relaxation will be under our strict monitoring to ensure the appropriate depth of anaesthesia and the success rate and accuracy of monitoring of TceMEPs during the operation. In addition, we will use the muscle relaxant antagonist Sugammadex free of charge for all subjects who use muscle relaxants after the operation, which will significantly reduce the occurrence of postoperative muscle relaxation and reduce complications related to muscle relaxation. The results obtained from this study may guide the use and management of intraoperative muscle relaxants in the future and bring benefits to patients undergoing similar operations.

8. POSSIBLE ADVERSE REACTIONS, RISKS and DISCOMFORT, INCONVENIENCES of PARTICIPATING in the STUDY

The adverse reactions of Sugammadex include nausea and vomiting, hypertension, and tachycardia. In this study, the dosage of Sugammadex is small and will not cause obvious adverse reactions. We have also formulated a detailed response plan if nausea and vomiting occur after surgery, you will be given antiemetic drugs; hypertension and tachycardia can be relieved by giving antihypertensive drugs.

If antagonistic drugs are not used during surgery, there may be a risk of failure in motor evoked potential monitoring. For this situation we have formulated the following remedy measures: ① Notify the surgeon and adjust the operation manipulation that may cause the failure of TceMEPs monitoring; ② Monitor the degree of muscle relaxation, and give appropriate amount of Sugammadex to maintain TOFr≥90%③Correct TceMEPs monitoring technical parameters, such as stimulation intensity, stimulation interval time and number of stimulation strings, etc.; ④ Correct Physiological parameter abnormalities that may occur during the operation, such as blood pressure, hemoglobin concentration, body temperature, arterial carbon dioxide partial pressure and body position, etc.; ⑤Adjust the depth of anesthesia under the guidance of the BIS value, and ensure that the BIS is ≤50 to avoid intraoperative awareness. The above plan will ensure your safety and the smooth progress of the operation.

If your health does suffer from research-related damage due to participation in this research, please notify the doctor immediately, who will be responsible for taking appropriate treatment measures for you. The sponsor, Beijing Tiatan Hospital, will bear the cost of treatment and provide you with corresponding financial compensation in accordance with relevant national regulations.Even if you have signed this informed consent form, you still retain all your legal rights.

9. OTHER TREATMENT CHOICE

If you do not participate in this study, you can choose your anesthesia treatment according to your anesthesiologist's suggestion.

10. YOU MAY VOLUNTARILY CHOOSE TO PARTICIPATE in the STUDY and WITHDRAW from the STUDY

Whether to participate in the study is entirely up to you. You may refuse to participate in the study or withdraw from the study at any time during the study, which will not affect your relationship with your doctor or affect your medical service or other benefits.

Before making decision, you can discuss with your family or friend， or you can talk with your doctor for any question, until you fully understand this study.

11. RELATED EXPENSES

Anesthetic drugs and surgical procedures are not free of charge. If you combine the treatment and examination required for other diseases, and if the treatment fails, the cost of changing to other treatment is not free of charge. If any medical expense happened due to adverse event, you will be exempted from the charge.

12. CONFIDENTIALITY of PERSONAL INFORMATION

Your medical records (study records /CRF, lab sheets, etc.) will be kept intact at the hospital. Your doctor will record the results of tests and other tests on your medical record. Researchers, ethics committees, and drug regulators will be allowed access to your medical records. Any public reports on the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical data within the law.

13. HOW TO GET MORE INFORMATION?

You can ask any questions about this study at any time and get answers. Your anesthesiologist will be ready to answer any of your questions before, during and after the study.

14. HOW THE STUDY MAY EFFECT YOUR LIFE?

You may feel the visit and examination uncomfortable and special arrangement is needed. You can consult your doctor in any steps of the study.

15. CONSULTING

If you have any related questions, please contact Dr. Jian Minyu (phone: 010-59976656 or cell phone: 13522550438).

If you have any concerns about your personal benefits, or you want to complain or express your concerns about the study, please contact the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (phone：010-59975178, email: ttyyirb@163.com).

SINGATURE PAGE OF AGREEMENT

Study title: Effect of Intraoperative Muscle Relaxation Reversal on the Success Rate of Motor Evoked Potential recording in Patients Undergoing Spinal Surgery

Principal Investigator: Ruquan Han, Beijing Tiantan Hospital, CMU

DECLARATION of CONSENT

I have read the introduction about the study above and have the opportunity to discuss with doctors and ask the questions about the study. All my questions have been answered satisfactorily.

I am aware of the possible risk and benefits of participating in this study. I know that participating in the study is voluntary. I have taken it into full consideration, and known that:

- I can ask my doctor for more information at any time.
- I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

I am also aware that if I withdraw from the study, especially if I withdraw due to medication, it will be of great benefit to the whole study if I tell my doctor about my condition and complete the corresponding physical examination and physical and chemical inspection.

If I need to take any other medication due to a change in my condition, I will consult my doctor beforehand or tell him afterwards truthfully.

I agree that the ethics committee of the drug regulatory authority or the representative of the sponsor may have access to my research information.

I will be provided with a signed and dated copy of the informed consent.

In the end, I agreed to participate in the study and promised to follow my doctors' advice as much as possible.

Signature of patient/legal relative:_____

Relation: _____

Date: _____ **(yyyy/mm/dd)**

I confirm that I have explained the details of the trial to the patients, including its rights and possible benefits and risks, and have given them a signed copy of the informed consent.

Signature of doctor:_____

Date: _____ **(yyyy/mm/dd)**

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2/17
	2b	All items from the World Health Organization Trial Registration Data Set	2/17
Protocol version	3	Date and version identifier	/
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	11
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____/_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____3-4_____
	6b	Explanation for choice of comparators	_____3-4_____
Objectives	7	Specific objectives or hypotheses	_____4_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____5_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____5_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	____5_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____5-6____

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____7___
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____/____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____7_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____7-8_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____/_____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____8_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____/_____

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5-6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5-7

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____ 8____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____8-9____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____8-9____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____8-9____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____/_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____/_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____9____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____/_____

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	/
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	/
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	/
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9

	31b	Authorship eligibility guidelines and any intended use of professional writers	_____/_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____9_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____/_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____/_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.