

# Study Protocol

Official Title : Comparison of Operating Conditions, Postoperative Recovery and Overall Satisfaction Between Deep and Restricted Neuromuscular Blockade for Spinal Surgery Under General Anesthesia

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## Protocol of the Research

<b>1.1 Objectives &amp; Hypotheses</b>	<p><b>* Objectives</b></p> <p><b>Primary Outcome Measure(s):</b></p> <ol style="list-style-type: none"> <li>1. Mean Value of Peak Inspiratory Pressure [Time Frame: Every 15 minutes during anesthesia]</li> </ol> <p><b>Secondary Outcome Measure(s):</b></p> <ol style="list-style-type: none"> <li>2. Mean Value of Pressure of Back Muscle Retractor [Time Frame: Every 15 minutes during the placement of the retractor]</li> <li>3. Overall Satisfaction of Surgeons for the Surgical Condition [Time Frame: After surgery]</li> <li>4. The Muscle Tone [Time Frame: at the screw insertion through the pedicle of spine during surgery]</li> <li>5. The Number of Body Movements [Time Frame: Throughout the surgery]</li> <li>6. The Degree of Bleeding [Time Frame: Throughout the surgery]</li> <li>7. Recovery Time (Time to Reach Sedation Score 5 at Post-anesthesia Care Unit (PACU). [Time Frame: every 10 min for 1 hour at PACU.]</li> <li>8. Adverse Events [Time Frame: during the postoperative 24 hours]</li> </ol> <p><b>* Clinical hypotheses</b></p> <p>(1) Mean value of peak inspiratory pressure (PIP) is lower in deep NMB group than in restricted NMB group. The higher PIP in restricted NMB group is related to the more surgical bleeding compared to deep NMB group.</p> <p>(2) Operating conditions including the number of body movement, degree of bleeding and muscle tone in deep NMB group are superior to restricted NMB group.</p> <p>(3) Overall satisfaction of surgeons in deep NMB group is superior to restricted NMB group.</p>
<b>1.2 Background &amp; Rationale, Significance of Selected Topic</b>	<p>Current standard of anesthesia in Motor Evoked Potential (MEP) monitored neurospinal surgeries is TIVA (total intravenous anesthesia) without muscle relaxant or with shallow NMB because deep NMB prevents monitoring of MEPs during surgery.</p> <p>However, there are several disadvantages associated with surgical and anesthetic conditions in MEP monitored surgeries.</p> <p>We aim to investigate operating conditions, postoperative recovery and overall satisfaction of surgeons between deep NMB group and restricted NMB for MEP not monitoring spinal surgery under general anesthesia. We expect that this study can present good surgical conditions, postoperative recovery outcomes and overall satisfaction of surgeons in deep NMB group, thereby proving the advantages of deep NMB as well as flaws of restricted NMB in spine surgeries.</p> <p>In this study, channeling bias is not likely to be problematic, as the establishment of group and the indications or criteria of MEP monitoring in spine surgeries are mainly associated with the patient's clinical signs and pre-existing motor deficits</p>

	<p>rather than the extent or difficulty of surgery. However, channeling regarding to the group treatment according to MEP monitoring can make this study be a non-randomized trial and certain patient differences would be expected between treatment groups. Therefore, we will enroll patients undergoing spinal surgery without MEP monitoring to determine the value of deep block on surgical and anesthetic condition.</p>
<p><b>1.3 Study Design</b></p>	<p><b>Group treatment (Arms):</b> Group RB, group treated restricted NMB; Group DB, group treated with deep NMB → randomized allocation (subjects: MEP not monitored surgeries)</p> <p><b>Inclusion criteria:</b> Ninety ASA class I–II adults, aged 18-75 years, scheduled for elective spinal surgery (lumbar surgeries which have lesions no more than 3 spinal levels and not monitored by MEP) of duration &gt;1 hour and prone position under TIVA</p> <p><b>Exclusion criteria:</b> Pregnancy, the receipt of medication known to interfere with neuromuscular blockade, diseases affecting neuromuscular transmission, and the history of hypersensitivity on rocuronium or sugammadex. The patients who will have hemodynamic instability, mean blood pressure increase or fall of &gt; 30% from baseline (lasting for more than 5min), and blood loss &gt; 1 L during surgery, and MEP monitored surgeries.</p> <p><b>Monitoring devices:</b> An electrocardiograph, pulse oximetry probe, esophageal temperature probe, entropy sensor (Datex Ohmeda) and noninvasive blood pressure cuff or invasive arterial and central vein lines will be applied to patients before or after anesthesia induction. The neuromuscular blockade will be monitored with a train-of-four (TOF, frequency 2 Hz, current 50 mA, interval 15 s) using an accelerator device (TOF-Watch SX; Organon Ltd, Ireland). The stimulation electrodes will be placed on the wrist at the level of the ulnar nerve, and the accelerometer will be placed at the distal part of the thumb. The skin temperature on the patient’s thenar will be maintained above 32°C throughout the study by wrapping the arm in cotton. The TOF ratio (T4/T1) and T1 value will be displayed on the screen and recorded. State entropy will be used as a guide for anesthetic depth and it will be maintained at 40 to 60 during surgery.</p>
<p><b>1.4 Study Flowchart</b></p>	<pre> graph TD     A[Patients Enrollment (n=90)] --&gt; B[Group DB (n=45)]     A --&gt; C[Group RB (n=45)]     B --- B_text["* NMB strategy: - rocuronium 1 mg/kg for induction - maintain deep NMB (TOF count 0, PTC of 1-2)"]     C --- C_text["* NMB strategy: - rocuronium 1 mg/kg for induction - use of <u>sugammadex to reverse the NMB 10 min after position change (supine → prone)</u> and thereafter, maintain the state of no more use of additional muscle relaxant"]   </pre>

	<p style="text-align: center;"><b>Operation condition assessment</b></p> <ol style="list-style-type: none"> <li>1) airway pressure (peak inspiratory pressure)</li> <li>2) pressure of back muscle retractor</li> <li>3) the number of body movements</li> <li>4) the degree of bleeding of each patient scaled by surgeons</li> <li>5) the muscle tone of each patient scaled by surgeons</li> </ol> <div style="display: flex; justify-content: space-around; margin-top: 10px;"> <div style="border: 1px solid black; padding: 5px; width: 45%;"> <p style="text-align: center;"><b>Reversal of NMB</b></p> <p>Sugammadex 4 mg/kg at the end of the surgery</p> </div> <div style="border: 1px solid black; padding: 5px; width: 45%; background-color: #f8d7da;"> <p style="text-align: center;"><b>Reversal of NMB</b></p> <p>No reversal agent; but if TOF ratio &lt; 0.9 pyridostigmine 10 mg</p> </div> </div> <div style="border: 1px solid black; padding: 10px; margin-top: 10px; text-align: center;"> <p><b>Postoperative assessment</b></p> <ul style="list-style-type: none"> <li>- recovery time</li> <li>- occurrence of adverse events</li> <li>- overall satisfaction of surgeons</li> </ul> </div>	
<p><b>1.5 Study Procedures</b></p>	<p><b>* Blinding and measure of outcomes</b></p> <p>· A double blinded approach will be used in this trial: randomization for group allocation and allocation concealment will be kept in this study. In the operating room, induction and maintenance (including the operation of TOF-Watch) of anesthesia will be performed by independent anesthesiologists not involved in the study and they are not blinded to the group allocation of patients. However, all surgeons will be blinded and so the evaluation of muscle tone of each patient scaled by surgeons will be blinded. Also, after the end of surgery, a blinded, independent investigator will assess the patients during the emergence and recovery phases. Postoperative outcomes including recovery time and surgeon satisfaction will be measured by the investigator blinded to the group assignment.</p> <ul style="list-style-type: none"> <li>➔ If the patients show any body movement during surgery or if surgeons express any complaint about muscle tone (the muscle tone: grade 3), rescue rocuronium 5 mg will be administered and the number of body movements and rescue rocuronium administration (dose) will be recorded.</li> <li>➔ The extubation criteria are as follows: TOF ratio &gt; 0.9, BIS &gt; 70, regular respiratory pattern, tidal volume of at least 5 ml/kg and SpO<sub>2</sub> &gt; 95% when the patient breathes spontaneously.</li> </ul> <p><b>* Drug treatment</b></p> <ul style="list-style-type: none"> <li>· Premedication: midazolam 2 mg, i.m (in all patients)</li> <li>· Induction: In all patients, after lidocaine 40 mg, i.v, effect-site concentration (CE) of propofol will be increased stepwise from the initial CE of 2.0 µg/mL until loss of the eyelash reflex (or arrival of state entropy less than 60), and then the TOF-Watch will be calibrated using the automatic calibrating procedure as soon as the patient is asleep. The first response in the TOF sequence (T1) will be defined as the baseline value to which all subsequent responses are compared. Effect-site concentration of remifentanyl will be then fixed to 1.5 ng/mL and rocuronium 1 mg/kg will be injected and the patients will be tracheally intubated at arrival of minimum T1 height.</li> </ul>	

	<p>· Ventilator settings: Tidal volume 8 mL/kg, respiratory rate initially 10 to 12 breaths/min, positive end-expiratory pressure (PEEP) 4 cmH<sub>2</sub>O and inspiratory-to-expiratory time ratio 1:2. Mechanical ventilation (respiratory rate) will be adjusted to maintain an end-tidal partial pressure of carbon dioxide at between 30 and 35 mmHg during surgery.</p> <p>· Maintenance: The patients will be allocated to one of the 2 groups receiving either DEEP NMB (group DB) or RESTRICTED NMB (group RB) according to the assignment using a computer random number generator.</p> <p>· NMB: In the group DB, rocuronium will be administered to maintain deep NMB (TOF count 0, PTC of 1-2 twitches) until the end of surgery and the reversal of NMB will be performed by sugammadex 4 mg/kg.</p> <p>In the group RB, sugammadex will be administered according to the prescribing indications (4 mg/kg for deep NMB state or 2 mg/kg for moderate NMB or less) to reverse the NMB 10 min after position change (10 min after placing the patient prone). Thereafter, muscle relaxants will not be injected any more throughout the surgery except the following situations: If the patients show any body movement during surgery or if surgeons express any complaint about muscle tone (the muscle tone: grade 3), rescue rocuronium 5 mg will be administered and the number of body movements and rescue rocuronium administration (dose) will be recorded.</p> <p><b>* Anesthesia &amp; management of hemodynamics</b></p> <p>After induction, the infusion paradigm of propofol and remifentanyl for both the groups is as follows: remifentanyl will be infused with a constant rate of CE 1.5 ng/mL, and the CE of propofol at loss of the eyelash reflex will be maintained. The most preferred BIS value of each patient was around 50, the CE of propofol will be titrated upwards or downwards 0.5 to 1.0 µg/mL each time if the BIS keeps increasing or decreasing. The BIS level of both the groups will be kept at 40 to 60 during surgery, which was regarded as the proper sedative depth. The infusion will be stopped at the time of skin suture. Ephedrine 4 mg or nicardipine 0.5 mg will be injected intravenously if the mean arterial pressure falls or increases by &gt; 30% relative to baseline. Glycopyrrolate 0.2 mg will be given if the heart rate falls below 50 beats per minute. At the end of surgery, the TOF count or ratio will be recorded, and after patients are turned supine, in the group DB, sugammadex 4 mg/kg will be administered for the reversal of NMB. In the group RB, pyridostigmine 10 mg and glycopyrrolate 0.4 mg will be administered only if TOF ratio is &lt; 0.9.</p>
<p><b>1.6 References</b></p>	<p>Chen N, Zhou SJ, Yan HC, Xie Z. Influence of neuromuscular blockade on motor evoked potential of forearm muscles. <i>Zhonghua Yi Xue Za Zhi</i> 2009 24;89(7):445-8.</p> <p>Edmonds HL Jr, Paloheimo MP, Backman MH, Johnson JR, Holt RT, Shields CB. Transcranial magnetic motor evoked potentials (tcMMEP) for functional monitoring of motor pathways during scoliosis surgery. <i>Spine (Phila Pa 1976)</i> 1989;14(7):683-6.</p> <p>Hashimoto Y, Gotanda Y, Ito T, Ushijima K. Recovery from rocuronium by sugammadex does not affect motor evoked potentials. <i>Masui</i> 2011;60(8):968-71.</p> <p>Kalkman CJ, Drummond JC, Kennelly NA, Patel PM, Partridge BL. Intraoperative monitoring of tibialis anterior muscle motor evoked responses to transcranial electrical stimulation during partial neuromuscular blockade. <i>Anesth</i></p>

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