Epidural Administration of Ropivacaine Reduces the Amplitude of Transcranial Electrical Motor–Evoked Potentials: A Double-Blinded, Randomized, Controlled Trial

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BACKGROUND: An epidurally administered local anesthetic acts primarily on the epidural nerve roots and can act directly on the spinal cord through the dural sleeve. We hypothesized that epidurally administered ropivacaine would reduce the amplitude of transcranial electrical motor-evoked potentials by blocking nerve conduction in the spinal cord. Therefore, we conducted a double-blind, randomized, controlled trial.

METHODS: Thirty adult patients who underwent lung surgery were randomly allocated to 1 of 3 groups, based on the ropivacaine concentration: the 0.2% group, the 0.375% group, and the 0.75% group. The attending anesthesiologists, neurophysiologists, and patients were blinded to the allocation. The epidural catheter was inserted at the T5–6 or T6–7 interspace by a paravertebral approach, using the loss of resistance technique with normal saline. General anesthesia was induced and maintained using propofol and remifentanil. Transcranial electrical motor-evoked potentials were elicited by a train of 5 pulses with an interstimulus interval of 2 milliseconds by using a constant-voltage stimulator and were recorded from the tibialis anterior muscle. Somatosensory-evoked potentials (SSEPs) were evoked by electrical tibial nerve stimulation at the popliteal fossa. After measuring the baseline values of these evoked potentials, 10 mL of epidural ropivacaine was administered at the 0.2%, 0.375%, or 0.75% concentration. The baseline amplitudes and latencies recorded before administering ropivacaine were defined as 100%. Our primary end point was the relative amplitude of the motor-evoked potentials at 60 minutes after the epidural administration of ropivacaine. We analyzed the amplitudes and latencies of these evoked potentials by using the Kruskal-Wallis test and used the Dunn multiple comparison test as the post hoc test for statistical analysis.

RESULTS: The data are expressed as the median (interquartile range). Sixty minutes after epidurally administering ropivacaine, the motor-evoked potential amplitude was lower in the 0.75% group (7% [3%–18%], between-group difference P < .001) and in the 0.375% group (52% [43%–59%]) compared to that in the 0.2% group (96% [89%–105%]). The latency of SSEP was longer in the 0.75% group compared to that in the 0.2% group, but the amplitude was unaffected.

CONCLUSIONS: Epidurally administered high-dose ropivacaine lowered the amplitude of motor-evoked potentials and prolonged the onset latencies of motor-evoked potentials and SSEPs compared to those in the low-dose group. High-dose ropivacaine can act on the motor pathway through the dura mater. (Anesth Analg XXX;XXX:00-00)

KEY POINTS

- **Question:** Would high-dose epidural ropivacaine reduce the amplitude of transcranial electrical motor–evoked potential via nerve conduction blockade on the corticospinal tract?
- **Findings:** High-dose ropivacaine lowered the amplitude of motor-evoked potential compared to low-dose ropivacaine.
- **Meaning:** High-dose ropivacaine, which could diffuse into cerebrospinal fluid, may act on the motor pathway in the spinal cord.
The mechanisms of epidural anesthesia may be more complex than those of a peripheral nerve block. A general assumption is that the epidural administration of a local anesthetic exerts its analgesic action by blocking the conduction of nociceptive sensation on the spinal roots in the epidural space. Previous studies also suggest that local anesthetics administered to the epidural space diffuse to the intrathecal space through the dural sleeves. They then act on the spinal cord because cerebrospinal fluid (CSF) concentrations of local anesthetics are elevated after epidural administration. In addition, local anesthetics block nerve conduction by blocking voltage-gated sodium channels and can inhibit excitatory neurotransmission in the spinal cord. Hence, local anesthetics administered in the epidural space may exert their effect by inhibiting spinal cord conduction, including the motor and sensory pathways, and by inhibiting excitatory neurotransmission in spinal interneurons.

Recent reports demonstrate that intraoperative multimodal spinal cord monitoring can increase the accuracy of detecting spinal cord injury. In particular, motor-evoked potentials (MEPs) have been widely used because of their high sensitivity for detecting neurologic injury. Therefore, MEPs have an important role in intraoperative monitoring to prevent motor dysfunction.

Several human studies have used neurophysiologic monitoring to demonstrate whether epidural anesthesia would act directly on the spinal cord. The findings of the previous studies indicate that the epidural administration of bupivacaine (0.125% and 0.5%) or ropivacaine (0.2%) did not significantly affect the amplitudes or latencies of somatosensory-evoked potentials (SSEPs), although only slight prolongation of the latency occurred. However, with regard to the action of epidural anesthesia on MEPs, only 1 case report demonstrated that epidural ropivacaine (0.5%) extinguished MEPs 30 minutes after its administration. Based on these findings, epidural anesthesia may act on the spinal cord, especially on the motor pathway.

We, therefore, hypothesized that high-dose epidural ropivacaine would reduce the amplitude of transcranial electrical MEPs via nerve conduction blockade on the corticospinal tract. The purpose of this double-blinded, randomized, controlled trial was to examine the effect of epidural ropivacaine administered at the midthoracic level on the amplitude of MEPs.

METHODS
This double-blinded, randomized, controlled trial was approved by the ethics committee of Niigata University (Niigata, Japan; approval no. 2015-1624) with mention in the application form that MEP monitoring is usually safe and the measurement had a small risk for complications (eg, bite injury, seizure) for the participants. The trial was registered before patient enrollment in the University Hospital Medical Information Network Clinical Trials Registry (Tokyo, Japan; registration no. UMIN000012371, registered by Toshiyuki Tobita on November 21, 2013). We conducted this study at Niigata University Medical and Dental Hospital (Niigata, Japan). We enrolled patients who were scheduled to undergo lung lobectomy or segmentectomy between January and October 2014. Written informed consent was obtained from all participants before their recruitment into the study. This article adheres to the applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines.

The exclusion criteria were (1) age <20 or >80 years, (2) inability to communicate, (3) contraindications to the drugs used in the study, (4) contraindications to epidural anesthesia, (5) a preexisting motor or sensory disturbance before surgery, (6) history of emergency surgery, (7) an estimated surgery time <2 hours, (8) not willing to participate, and (9) the anesthetic management using the study protocol deemed inappropriate by the attending anesthesiologist. We also excluded patients from the analysis when the attending anesthesiologist suspected that epidural analgesia had been ineffective, such as patients with severe postoperative pain or patients without any anesthetized area, confirmed by cold stimulation, just after emergence from anesthesia.

Randomization
We used a computer-generated simple randomization program to randomly assign participants to 3 groups in a 1:1:1 ratio, based on the ropivacaine concentration (ie, 0.2%, 0.375%, and 0.75%). The research assistant used a research randomizer that is available at https://www.randomizer.org. The randomization allocation table was concealed in sealed, prenumbered, and opaque envelopes. The research pharmacist kept these envelopes in a locked box installed in the in-hospital pharmacy throughout the study.

The anesthesiologist, who was independent of the study, was provided a syringe filled with 10 mL of the different concentrations of ropivacaine (150 mg/20 mL, Anapeine; Aspen, Tokyo, Japan), based on the

GLOSSARY
BIS = bispectral index; CMAP = compound muscle action potential; CONSORT = Consolidated Standards of Reporting Trials; CSF = cerebrospinal fluid; MEP = motor-evoked potential; SSEP = somatosensory-evoked potential
allocation. The patients, attending anesthesiologists, neurophysiologists, and all clinical staff were blinded to the group assignment throughout the study.

**Neurophysiologic Monitoring**

The evoked potentials were recorded using an intraoperative neurophysiologic monitoring system (Neuropack MEB-2208; Nihon Kohden, Tokyo, Japan) and were evaluated by a neurophysiologist during the procedure.

A pair of 14.5-mm silver-plated disk electrodes were placed on the scalp 2 cm anterior to C3 (ie, cathode) and C4 (ie, anode), using the International 10-20 system, for transcranial electrical stimulation. MEP was elicited by a train of 5 pulses with an interstimulus interval of 2 milliseconds by using a constant-voltage stimulator (Multipulse stimulator D-185; Digitimer, Letchworth Garden City, United Kingdom). The MEP was recorded from the tibialis anterior muscle on the ipsilateral side of the surgery. The stimulus intensity was commenced at 300 V and increased in 50-V increments until no further increase in the MEP amplitude of the tibialis anterior muscle occurred (ie, supramaximal stimulation). The MEP was recorded from the skin by using adhesive gel Ag–AgCl electrodes (NM314YL; Nihon Kohden) placed over the muscle belly and the muscle tendon by using a bandpass filtration of 10–3000 Hz.

SSEP was recorded to measure the effect of epidural ropivacaine on the spinal sensory pathways. The SSEP was recorded using disk electrodes, which were placed at Cz′ (ie, 2 cm posterior to Cz) and referenced to A1 or A2, based on the International 10-20 system, by using a bandpass filtration of 10–1500 Hz. The SSEPs were elicited by stimulating the tibial nerve at the popliteal fossa through adhesive gel Ag–AgCl electrodes (NM314YL; Nihon Kohden) placed 2 cm anterior to C3 (ie, anode) and the muscle tendon by using a bandpass filtration of 10–3000 Hz.

The CMAP was evoked by stimulating the tibial nerve at the popliteal fossa. The CMAP was recorded from the tibialis anterior muscle MEP by using 500-µs pulses at a current intensity of 25–35 mA.

A compound muscle action potential (CMAP) was recorded to assess the conditions of the nerve conduction, neuromuscular junction, and the innervated muscle itself. The CMAP was evoked by stimulating the tibial nerve at the popliteal fossa. The CMAP was recorded from the tibialis anterior muscle MEP by using 500-µs pulses at a current intensity of 25–35 mA.

The peak-to-peak amplitudes and the onset latencies of the MEPs, SSEPs, and CMAPs recorded before the administration of ropivacaine were defined as the “baseline” amplitudes and latencies, respectively. The amplitudes and latencies were expressed as relative values (the baseline values were 100%).

**End Points**

Our primary end point was the amplitude of the MEP at 60 minutes after the epidural administration of ropivacaine. We defined the 0.2% group as the control group and compared the 0.2% group with the 0.375% group and the 0.75% group.

Our secondary end points were the amplitudes recorded at the other time points (ie, 30, 120, and 180 minutes), the onset latency of MEP, the amplitude of the CMAP, and the N35–P42 amplitude and the N35 latency of the SSEP. These amplitudes and latencies were expressed as relative values (the values before the administration of ropivacaine were defined as

General anesthesia was induced with propofol (4–5 µg/mL) using a target-controlled infusion pump (TE-371 Syringe Pump; Terumo, Tokyo, Japan) and a continuous infusion of remifentanil (0.2–0.5 µg·kg⁻¹·min⁻¹). Succinylcholine (0.7–1 mg/kg) was administered for the intubation of the double-lumen tube, but no additional muscle relaxants were used during the surgery. After inducing anesthesia, the doses of propofol and remifentanil were adjusted to maintain a bispectral index (BIS) value within the range of 40–60.

After applying the electrodes, the patient’s posture was changed to the lateral decubitus position. After the baseline values of the MEPs, SSEPs, and CMAPs were measured, an attending anesthesiologist administered 10 mL ropivacaine at 1 of 3 concentrations (ie, 0.2%, 0.375%, and 0.75%) through an epidural catheter. The MEPs, SSEPs, and CMAPs were recorded at 30, 60, 120, and 180 minutes after the epidural administration of ropivacaine.

During the study, we controlled the systolic and the diastolic blood pressure in the range of 85–140 and 40–90 mm Hg, respectively. Ephedrine or phentolamine was administered intravenously when the systolic blood pressure decreased below 85 mm Hg. The heart rate was maintained at 50–100 beats per minute. The lungs were ventilated to maintain an arterial carbon dioxide level of approximately 38–42 mm Hg. The saturation of percutaneous oxygen was maintained above 95% by using a mixture of air and oxygen. The bladder temperature was maintained at >36 °C.
The relative amplitude and latency changes in the MEP, SSEP, and CMAP were calculated as follows: relative value (%) = (absolute value/baseline value) × 100.

**Statistical Analysis**

We analyzed the amplitudes and latencies of MEP, SSEP, and CMAP using the Kruskal-Wallis test; the Dunn multiple comparison test was the post hoc test for statistical analysis. One-way analysis of variance and the Tukey test were used to analyze the hemodynamic parameters, BIS values, body temperature, and doses of propofol and remifentanil. A value of $P < .05$ was statistically significant. All statistical analyses were performed using GraphPad Prism 7.0 (GraphPad Software, San Diego, CA). The amplitudes and latencies of the MEPs and SSEPs and the amplitude of CMAPs were expressed as the median (interquartile ranges). Hemodynamic data and BIS values were expressed as the mean (standard deviation).

**Sample Size Calculation**

The sample size was calculated using G-power 3.1 software (Heinrich Heine University of Düsseldorf, Düsseldorf, Germany) based on the preliminary study. The analysis revealed that the mean (standard deviation) relative amplitude of MEP after a bolus administration of 0.75% ropivacaine was 22% (18%) of the baseline value. We considered that a 40% decrement in the MEP amplitude of the 0.75% group from the amplitude of the 0.2% group was a clinically significant difference. Therefore, we assumed that the mean (standard deviation) relative amplitude of MEP in the 0.2% group would be 62% (25%) of the baseline value. As a result, a sample size calculation determined that 8 patients per group were the smallest sample size required to demonstrate a difference with a statistical power of 0.9 and a type 1 error rate of 0.05 using an independent samples t test. After allowing for possible dropouts, 10 patients per group were enrolled.

**RESULTS**

Thirty patients were randomly allocated to 1 of 3 groups (Figure 1). Two patients were excluded from the analysis because of failed epidural anesthesia: they had severe pain and no verified sensory block when they emerged from anesthesia. Another patient was excluded because we could not record evoked potentials on account of a malfunction in the neurophysiologic monitoring system. We could not record the MEP at 180 minutes in 3 patients (1 patient in each group) or at 90, 120, and 180 minutes in 1 patient in the 0.75% group because their surgeries were completed before these time points. The baseline characteristics and perioperative data of the study participants are shown in Table 1.

At 60 minutes, after the epidural administration of ropivacaine, the amplitudes of the MEPs were significantly lower in the 0.375% group (52% [43%–59%], $n = 9$, $P = .041$) and the 0.75% group (7% [3%–18%], $n = 8$, $P < .001$), compared to those of the 0.2% group (96% [89%–105%], $n = 10$) (Figure 2 and Table 2). The onset latencies of the MEPs were longer in the 0.75% group (121% [113%–138%]), compared to those of the 0.2% group.
The amplitude of the SSEP did not differ between the 3 groups. However, the latencies of the SSEPs were significantly longer in the 0.75% group (109% [108%–113%], P = .0053) at 60 minutes after ropivacaine administration (Table 3; Supplemental Digital Content, Figure 1, http://links.lww.com/AA/D213).

At 60 minutes after ropivacaine administration, the amplitudes of the CMAP did not differ among the 3 groups: 103% [66%–114%] in the 0.2% group; 110% [100%–116%] in the 0.375% group; and 100% [79%–107%] in the 0.75% group (Supplemental Digital Content, Table 1, http://links.lww.com/AA/D213). No significant differences existed between the 3 groups in the doses of propofol or remifentanil used (Table 4). No significant differences existed between the 3 groups in the systolic/diastolic blood pressure, heart rate, BIS value, and body temperature.

**Table 1. Baseline Characteristics and Perioperative Data of the Study Participants**

<table>
<thead>
<tr>
<th></th>
<th>0.2%</th>
<th>0.375%</th>
<th>0.75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, No.</td>
<td>6/4</td>
<td>4/5</td>
<td>3/5</td>
</tr>
<tr>
<td>Age, y</td>
<td>69 (4.5)</td>
<td>68 (5.4)</td>
<td>69 (7.2)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>160 (9.9)</td>
<td>157 (13.0)</td>
<td>155 (6.6)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>60 (12)</td>
<td>55 (12)</td>
<td>60 (7)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.1 (2.6)</td>
<td>22.2 (3.2)</td>
<td>25.0 (3.0)</td>
</tr>
<tr>
<td>ASA-PS; I/II, No.</td>
<td>0/10</td>
<td>1/8</td>
<td>0/8</td>
</tr>
<tr>
<td>Operated side; left/right, No.</td>
<td>3/7</td>
<td>5/4</td>
<td>5/3</td>
</tr>
<tr>
<td>Procedure; partial resection/segmentectomy/lobectomy, No.</td>
<td>0/3/7</td>
<td>0/2/7</td>
<td>1/4/3</td>
</tr>
<tr>
<td>Blood loss; median (range), mL</td>
<td>95 [10–1735]</td>
<td>75 [10–255]</td>
<td>60 [10–490]</td>
</tr>
<tr>
<td>Operation time, min</td>
<td>202 (39)</td>
<td>204 (44)</td>
<td>155 (42)</td>
</tr>
<tr>
<td>Anesthesia time, min</td>
<td>282 (38)</td>
<td>284 (45)</td>
<td>221 (89)</td>
</tr>
</tbody>
</table>

The data are presented as the mean (standard deviation), median [interquartile range], or number. Abbreviation: ASA-PS, American Society of Anesthesiologists physical status.
DISCUSSION

We demonstrated that the amplitudes of the MEPs were lower, and the latencies of the MEPs and SSEPs were longer in the high-dose epidural ropivacaine groups, compared to those in the low-dose ropivacaine group; in contrast, there were no significant effects on the amplitude of the CMAP. Our results suggest that high-dose epidural ropivacaine affects the motor and sensory pathways in the spinal cord.

The MEP amplitude is reduced with the inhibition of the motor pathway. The tibialis anterior muscle is innervated by the deep peroneal nerve, which is typically derived from the L4, L5, and S1 nerve roots. In the present study, we could not detect statistically significant differences in the relative amplitude of the CMAP between the groups. Therefore, it is suggested that the peroneal nerve, neuromuscular junction, and tibialis anterior muscle are unlikely to be the primary site of action, causing the differences in the MEP amplitudes between the groups. Furthermore, thoracic epidural ropivacaine cannot spread to the motor cortex, except for the systemic action of ropivacaine.

Table 2. The Relative Amplitudes and Onset Latencies of MEPs

<table>
<thead>
<tr>
<th>Relative Amplitude of MEP</th>
<th>0.2%</th>
<th>0.375%</th>
<th>0.75%</th>
<th>P</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Relative Onset Latency of MEP</th>
<th>0.2%</th>
<th>0.375%</th>
<th>0.75%</th>
<th>P</th>
</tr>
</thead>
</table>

The data are presented as the median [interquartile range]. The P values were calculated using the Kruskal-Wallis test and Dunn multiple comparison test as the post hoc test.

Abbreviation: MEP, motor-evoked potential.

*A significant difference exists between the 0.2% group and the 0.75% group.

Table 3. The Relative Amplitudes and Latencies of the SSEPs

<table>
<thead>
<tr>
<th>Relative Amplitude (N35–P42) of SSEP</th>
<th>0.2%</th>
<th>0.375%</th>
<th>0.75%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>180 min</td>
<td>113 [59–124]</td>
<td>79 [77–82]</td>
<td>95 [77–110]</td>
<td>.54</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative Latency (N35) of SSEP</th>
<th>0.2%</th>
<th>0.375%</th>
<th>0.75%</th>
<th>P</th>
</tr>
</thead>
</table>

The data are presented as the median [interquartile range]. The P value was calculated using the Kruskal-Wallis test and Dunn multiple comparison test as the post hoc test.

Abbreviation: SSEP, somatosensory-evoked potential.

*Pairwise between-group comparisons were not significant.

*A significant difference exists between the 0.2% group and the 0.75% group.

Table 4. A Comparison of the Doses of Propofol and Remifentanil

<table>
<thead>
<tr>
<th>Propofol (µg/mL)</th>
<th>0.2%</th>
<th>0.375%</th>
<th>0.75%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.9 (0.4)</td>
<td>2.7 (0.4)</td>
<td>2.6 (0.3)</td>
<td>.34</td>
</tr>
<tr>
<td>30 min</td>
<td>2.9 (0.5)</td>
<td>2.7 (0.5)</td>
<td>2.6 (0.3)</td>
<td>.24</td>
</tr>
<tr>
<td>60 min</td>
<td>2.9 (0.4)</td>
<td>2.6 (0.5)</td>
<td>2.6 (0.4)</td>
<td>.33</td>
</tr>
<tr>
<td>120 min</td>
<td>2.9 (0.4)</td>
<td>2.6 (0.4)</td>
<td>2.5 (0.3)</td>
<td>.07</td>
</tr>
<tr>
<td>180 min</td>
<td>2.8 (0.3)</td>
<td>2.7 (0.3)</td>
<td>2.6 (0.3)</td>
<td>.31</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Remifentanil (µg/kg/min)</th>
<th>0.2%</th>
<th>0.375%</th>
<th>0.75%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.23 (0.07)</td>
<td>0.33 (0.20)</td>
<td>0.23 (0.06)</td>
<td>.17</td>
</tr>
<tr>
<td>30 min</td>
<td>0.30 (0.10)</td>
<td>0.30 (0.11)</td>
<td>0.25 (0.04)</td>
<td>.45</td>
</tr>
<tr>
<td>60 min</td>
<td>0.34 (0.12)</td>
<td>0.32 (0.11)</td>
<td>0.26 (0.04)</td>
<td>.24</td>
</tr>
<tr>
<td>120 min</td>
<td>0.37 (0.14)</td>
<td>0.33 (0.09)</td>
<td>0.29 (0.06)</td>
<td>.30</td>
</tr>
<tr>
<td>180 min</td>
<td>0.37 (0.18)</td>
<td>0.30 (0.15)</td>
<td>0.23 (0.05)</td>
<td>.19</td>
</tr>
</tbody>
</table>

The data are presented as the mean (standard deviation). The P value was calculated using 1-way analysis of variance.
We had no data regarding the effect of systemic ropivacaine on the MEP. However, 1 study\textsuperscript{17} reported that systemic lidocaine did not affect MEP. Therefore, high-dose ropivacaine can act on the corticospinal tract of the spinal cord, ventral horn neurons, and/or spinal roots (L4–S1) in the epidural space.

In this study, we administered 10 mL of ropivacaine through an epidural catheter inserted at the T5–6 or T6–7 interspace. Previous reports show that the mean caudal spread of the analgesic area after administering 6–8 mL of 0.75% ropivacaine through the T2–3 or T3–4 interspace reached the T9–L3 dermatome with its peak effect at approximately 30 minutes after the administration.\textsuperscript{18,19} We believe that the significantly lower relative amplitude of the MEPs recorded from the tibialis anterior muscle could not be caused only by the nerve conduction block on the L4–S1 roots because, in the present study, the median relative amplitude of MEP after administering 0.2% ropivacaine was 96% of baseline. If 0.2% ropivacaine reached the lumbar nerve roots, the amplitude of MEP would be reduced from the baseline amplitude. Some research indicates that 0.2% ropivacaine causes motor weakness when administered to the lumbar epidural space.\textsuperscript{20} Therefore, our findings suggested that the entire dose of 0.2% ropivacaine did not reach the lumbar nerve roots. Therefore, we think that the suppressive effect of high-dose ropivacaine on the MEP was caused by a conduction block in the corticospinal tract rather than in the nerve roots.

Previous reports\textsuperscript{4,5} suggest that local anesthetics administered to epidural space can elevate their concentration in the CSF to the millimolar level. Some research indicates that 0.1 mM ropivacaine can inhibit tetrodotoxin-resistant sodium currents.\textsuperscript{21} Therefore, the CSF concentration of ropivacaine after epidural administration (approximately 0.3–3 mM)\textsuperscript{5} should be sufficient to block nerve conduction. These reports indicate that high-dose ropivacaine can block the motor pathway in the spinal cord. In addition, the time at which the maximum amplitude reduction of the MEP occurred after administering ropivacaine in the present study (ie, after 30–60 minutes) was similar to the time at which the peak CSF concentration of ropivacaine occurred in a previous animal study.\textsuperscript{5} Therefore, we believe that ropivacaine diffused into the CSF directly inhibited nerve conduction in the spinal cord, and thereby reduced the amplitude of the MEP.

Local anesthetics also interact with many membrane phospholipids and proteins, including various receptors. At the CSF concentration reached after the epidural administration of local anesthetics,\textsuperscript{1–6} ropivacaine and other local anesthetics can inhibit excitatory neurotransmission.\textsuperscript{7–11} Thus, in the present study, the inhibition of excitatory neurotransmission in ventral horn neurons by ropivacaine could be involved in the mechanisms of the reduction in the MEP amplitude.

Under some criteria, a positive SSEP change is defined as a >10% increase in the SSEP latency.\textsuperscript{22} In the present study, the relative SSEP latencies were longer in the 0.75% group, approximately 110% of the baseline value, compared to that in the 0.2% group. In addition, the relative MEP latencies were also longer in the 0.75% group, although a prolonged MEP latency is not used as a diagnostic criterion in intraoperative monitoring. Unlike the MEP amplitude, the SSEP amplitude did not become reduced after the administration of ropivacaine. Our results were similar to those of previous reports in which the amplitude and the latency of SSEP were not significantly changed after the thoracic epidural administration of bupivacaine.\textsuperscript{13,15} Because the motor and sensory pathways have distinct anatomies and vascular supplies, the ability of epidural ropivacaine to suppress especially the amplitude of MEP is not a surprising finding.\textsuperscript{23} Our results may reflect nerve conduction block on sensory and motor pathways in the spinal cord.

**Clinical Implication**

Epidural analgesia is a useful option for open thoracoabdominal aortic aneurysm repair\textsuperscript{24,25} and for complex spine surgery.\textsuperscript{26} However, intraoperative MEP monitoring is often required in these surgeries to prevent neurologic complications. Hence, the results of the present study suggest that an intraoperative bolus epidural administration of local anesthetics should be avoided until intraoperative neurophysiologic monitoring is completed. If epidural administration is necessary, low-dose local anesthetics (eg, 0.2% ropivacaine) should be used.

**Limitations**

Our study has some limitations. First, we did not confirm the effect of epidural anesthesia before surgery. However, postoperative epidural analgesia was provided effectively to all other participants except for the 2 excluded participants. Therefore, we believe that the epidural catheters were inserted accurately into the epidural space. Second, we could not demonstrate whether the reduction in the MEP amplitude caused by the administration of epidural ropivacaine would cause motor dysfunction because the participants were under the influence of general anesthesia when the action of ropivacaine reached its peak. Third, this study was not a placebo-controlled trial because of an ethical problem in that the epidural administration of placebo has the potential to disadvantage the patient regarding intra- and postoperative analgesia. To resolve the problem, we used low-dose ropivacaine as the control instead of a placebo. Therefore,
Epidural Ropivacaine Suppresses MEPs

we believe that our study is as valuable as a placebo-controlled trial. Fourth, a sample size was calculated based on the result of preliminary study comparing 2 groups, while we compared 3 groups in the present study. However, since we used the Dunn multiple comparison test for the post hoc test, we speculate that the statistical analysis performed for the primary endpoint was appropriate.

In conclusion, the epidural administration of high-dose ropivacaine lowered the relative amplitudes of the MEPs compared to that in the low-dose group. Our results suggested that epidural ropivacaine can act on the spinal cord through the dura mater. A bolus epidural administration of high-dose ropivacaine should be avoided when intraoperative MEP monitoring is necessary.

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REFERENCES

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