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Effects of rocuronium dosage on intraoperative neurophysiological monitoring in patients undergoing spinal surgery

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Abstract

What is known and objective: Intraoperative neurophysiological monitoring (IONM) has been widely used in clinical practice. Therefore, the influence of neuromuscular blockers essential for spinal anaesthesia on IONM is worthy of our attention, but no randomized study has evaluated the dose-response effect. This study investigated the effects of different doses of rocuronium bromide on the intraoperative monitoring of motor evoked potentials (MEPs).

Methods: We conducted a randomized, double-blind trial to assess the effects of three rocuronium bromide doses (6.0, 9.0, 12 $\mu g \cdot kg^{-1} \cdot min^{-1}$) combined with intravenous infusion of propofol 6–8 $mg \cdot kg^{-1} \cdot h^{-1}$ and remifentanil 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ on the amplitudes of somatosensory evoked potentials (SEPs) and MEPs at the time of the baseline recording (T_1), before pedicle screw placement (T_2) and before spinal canal decompression (T_3). Secondary outcomes included measurement of neuromuscular function, the occurrence of unexpected intraoperative body movement and recovery of spontaneous breathing.

Results and discussion: A total of 123 patients were enrolled, and 120 patients were ultimately analysed. No differences were observed in the amplitude of SEPs among the three groups ($p > 0.05$). The MEP amplitude differences at T_1, T_2 and T_3 in all limbs did not differ in patients receiving rocuronium at 6.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 9.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ($p > 0.05$). However, when rocuronium was administered at 12.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, MEP amplitudes at the time point T_3 were significantly attenuated compared with the time points T_1 and T_2 in both right upper limb and left lower limb ($p = 0.002$, $p = 0.025$, respectively). In patients treated with rocuronium 6.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, the incidence of unexpected body movement was significantly higher ($p = 0.026$), and the train-of-four count (TOF count) showed a significant increase at T_2 and T_3 ($p < 0.001$) compared to other doses.

Xueyong Zhang and Hongyu Hu are co-first author

Clinical trial registration: China Clinical Trial Registry. Registration number: ChiCTR1800016808

What is new and conclusion: Rocuronium bromide at a rate of 9.0 μg·kg^{-1}·min^{-1} provided suitable and adequate muscle relaxation without inhibiting IONM; thus, this dose is recommended for spinal surgery.

KEYWORDS
intraoperative neurophysiological monitoring, neuromuscular blockers, train-of-four, motor evoked potentials

1 | WHAT IS KNOWN AND OBJECTIVE

In recent years, intraoperative neurophysiological monitoring (IONM) has become a routine monitoring method for spinal surgeries.[1] Effective monitoring helps avoid intraoperative iatrogenic injuries to the spinal cord and nerves and reduce the risk of repeated surgery.[2-4] The combined monitoring of somatosensory evoked potentials (SEPs) and motor evoked potentials (MEPs) is exceptionally safe and effective.[2,5]

However, most anaesthetics have diverse effects on neurophysiological parameters, often in a dose-dependent manner,[6] and thereby affect the accuracy and clinical significance of the monitoring results. Neuromuscular blockers, widely used in clinical anaesthesia, can improve surgical conditions, reduce the difficulty of surgery and prevent iatrogenic injuries.[7,8] At the same time, studies have shown that neuromuscular blockers can significantly inhibit the amplitude of MEPs.[9,10] Previous studies have reported that in patients with normal neurological functions and baseline responses with sufficient amplitude, partial neuromuscular blockade produced acceptable results when T_1 was reduced to 10% to 20% of the baseline or the train-of-four (TOF) count was 2.[11] Currently, muscle-pine monitors are not widely used in clinical practice in China. According to Ko et al., continuous infusion of rocuronium effectively inhibited unexpected intraoperative body movement and spontaneous breathing of the patient while enabling MEP monitoring.[12] Therefore, it is essential to identify an appropriate maintenance dose of a muscle relaxant that ensures smooth progression of the operation without interfering with neurophysiological monitoring for spinal surgery.

In this study, we investigated the effects of different doses of rocuronium bromide combined with total intravenous anaesthesia to provide a basis for the appropriate dosage of neuromuscular blockers in patients undergoing spinal surgery with IONM. The primary outcomes included the amplitudes of SEPs and MEPs during surgery. The secondary outcomes included measurement of neuromuscular function, the occurrence of unexpected intraoperative body movement and recovery of spontaneous breathing.

2 | METHODS

2.1 | Patient eligibility

Patients who underwent spinal surgery under neurophysiological monitoring in our hospital between July 2018 and December 2019 were selected. Both male and female patients were enrolled. All patients were between 18 and 65 years of age, had a body mass index (BMI) of 18.9 to 24.9 kg m^{-2},[13] classified as American Society of Anesthesiologists (ASA) I or II and underwent surgery that lasted 2–3 h. The patients had normal liver and kidney functions, acid-base balance and electrolyte levels before surgery. The exclusion criteria were neuromuscular diseases, the use of any drugs known to interact with neuromuscular blockers (eg clindamycin, gentamicin, bupivacaine and chronic use of anticonvulsants),[14,15] diabetes and other endocrine diseases, and underlying diseases such as heart diseases, neuropathies, mental diseases and genetic diseases.

2.2 | Ethical approval and trial registration

This study was approved by the Medical Ethics Committee of Second Affiliated Hospital of Harbin Medical University (No. KY2018-290), and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrolment at the China Clinical Trial Registry (ChiCTR1800016808, Principal investigator: Wanchao Yang, Date of registration: 26 June 2018). This manuscript adheres to the applicable CONSORT guidelines.

2.3 | Study design and protocols

Patients were assigned to one of the treatment groups before surgery using computer-generated random numbers by one of the investigators (41 patients in each group): group A (rocuronium bromide infused from a pump at a dose of 6 μg·kg^{-1}·min^{-1} during maintenance of muscle relaxation); group B (rocuronium bromide 9 μg·kg^{-1}·min^{-}1); and group C (rocuronium bromide 12 μg·kg^{-1}·min^{-1}). The investigators and patients were unaware of group assignment at the time of recruitment. Anaesthesiologists administered anaesthetics according to the patient's group assignment.

The patients strictly fasted for eight hours before surgery, no liquid was allowed for four hours, and no preoperative drugs were administered. After entering the operation room, oxygen was administered to the patient from a mask, and two peripheral venous lines were prepared. The electrocardiogram (ECG), heart rate (HR), pulse oxygen saturation (SpO_2), noninvasive blood pressure (BP), mean arterial pressure (MAP), temperature and bispectral index (BIS) were monitored. In addition, a train-of-four (TOF)-Watch real-time muscle relaxation monitor (TOF-Watch®, Organon (Ireland) Ltd., Dublin, Ireland) was placed to monitor muscle relaxation. One of the peripheral venous lines was infused with sodium lactate Ringer's solution. All anaesthetics were infused through this line, and other solutions required during the surgery were infused through the other peripheral venous line. Anaesthesia was induced with midazolam 0.05–0.1 mg kg^{-1}, propofol 1–2 mg kg^{-1}, sufentanil 0.3–0.5 μg kg^{-1}, lidocaine 1–2 mg kg^{-1} and rocuronium bromide 0.6 mg kg^{-1}. Anaesthesia was maintained by intravenous infusion of propofol 6–8 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ and remifentanil 0.1–0.3 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$, and the BIS value was maintained at 40–60 until the end of the surgery. During the operation, vasoactive drugs were administered as needed, $P_{ET}CO_2$ was maintained within 35–45 mmHg by adjusting the respiratory rate, the MAP was maintained at 70–90 mmHg, the armpit temperature was maintained at 36.5–37.3°C, and the peak airway pressure was kept lower than 20 cmH_2O. Spinal cord function was monitored using a US NIM-Eclipse neuromonitoring system. After induction of anaesthesia, the monitoring electrodes, which were subcutaneous needle electrodes, were placed according to the international 10/20 system standard. SEPs were monitored with a constant-current single-phase pulse. Lower limb stimulation was performed at the tibial nerve, and the recording electrodes were Cz and Fz. Upper limb stimulation was performed at the median nerve and the ulnar nerve, and the recording electrodes were C3-Fz and C4-Fz. The stimulating intensity was 30 mA, and the stimulating frequency was 4.1 Hz. MEPs were monitored with transcranial electrical stimulation using a constant voltage stimulator. The stimulation electrodes were placed at the C3' and C4' positions and the recording electrodes were on the bilateral anterior tibialis, thenar and abductor pollicis brevis muscles. The stimulating voltage was 220 V. After recording the baseline MEPs and SEPs of IONM, rocuronium bromide was continuously infused by a pump until the start of spinal canal decompression. Postoperative muscle relaxant antagonist was administered as needed.

The amplitude of SEPs, the amplitude of MEPs and the TOF count were recorded at the following three time points: the baseline potential recording (T_1), immediately before pedicle screw placement (T_2) and immediately before spinal canal decompression (T_3). At the same time, unexpected intraoperative body movement and spontaneous breathing recovery of the patients were recorded. All the data were obtained by one of the investigators who did not know the patient group assignment. In this study, our primary outcomes were the amplitude of SEPs and MEPs, and the secondary results included the incidence of unexpected intraoperative body movement, recovery of spontaneous breathing and TOF count.

2.4 | Statistical analysis

Before the study, we estimated the sample size through a pilot study. Our primary outcome of this study was the amplitude of MEPs. Through the pilot study, we calculated the sample size by comparing MEP amplitudes at T_2 and T_3 of each limb with MEP amplitudes at T_1. The MEP amplitude increased by 74.7 on average, and the standard deviation was 126.18. The calculated sample size was 37.07 ($\alpha = 0.05$, $\beta = 0.05$). We concluded that 41 cases should be included in each group, considering 10% dropouts. All data were analysed using SPSS 19.0 statistical software. Average measurement data are presented as the mean ± standard deviation, while nonnormal data are presented as the median (interquartile range). The statistical significance of the differences between the data was assessed by the chi-square test or Fisher exact test for categorical variables and independent tests or related tests for continuous variables as appropriate. To examine if its distribution was normal, we used the Shapiro-Wilk test. P values less than 0.05 were considered statistically significant.

3 | RESULTS AND DISCUSSION

Initially, 123 patients were enrolled in this study. Three patients were excluded because they had been under anaesthesia for more than 30 min when the baseline potentials of IONM were recorded, which left 120 patients for the final study, with 40 patients in each group. The flow of subjects through the study is shown in Figure 1. There was no significant difference ($p > 0.05$) in overall patient profile among the three groups, including sex, age, height, weight, BMI and ASA grade. The details are provided in Table 1.

The primary results were as follows: the magnitude of the differences among the SEP amplitudes was similar at T_1, T_2 and T_3 in their respective groups ($p > 0.05$). The differences in MEP amplitude at T_1, T_2 and T_3 in all limbs did not reach statistical significance in either group A (rocuronium 6.0 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$) or group B (9.0 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$) ($p > 0.05$). However, in group C (rocuronium 12.0 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$), MEP amplitudes at time point T_3 were significantly attenuated compared with those at time points T_1 and T_2 in both the right upper limb and left lower limb ($p = 0.002$, $p = 0.025$, respectively). The details are listed in Table 2.

The secondary results were as follows: six patients in group A had unexpected body movement during the operation and one of them experienced a serious bite injury with visible bleeding from deep lacerations of the tongue and the lip requiring sutures. No patient in groups B or C had unexpected body movement during the whole procedure. One patient in group A experienced spontaneous respiratory recovery during the operation, while there was no such incidence in patients in groups B or C. The TOF counts showed significant differences among the three groups. In group B, the TOF counts were maintained at approximately 2. The details are listed in Table 3.

Comparison of the anaesthesia duration, operation time and three IONM time points among the three groups showed no significant difference ($p > 0.05$) (Table 4).

The goal of this study was to evaluate the effects of three doses of rocuronium bromide administered by continuous infusion on IONM. IONM, which can instantly reflect spinal cord and spinal nerve root functions, is widely used in spinal surgery. We infused rocuronium bromide at three doses within the range recommended

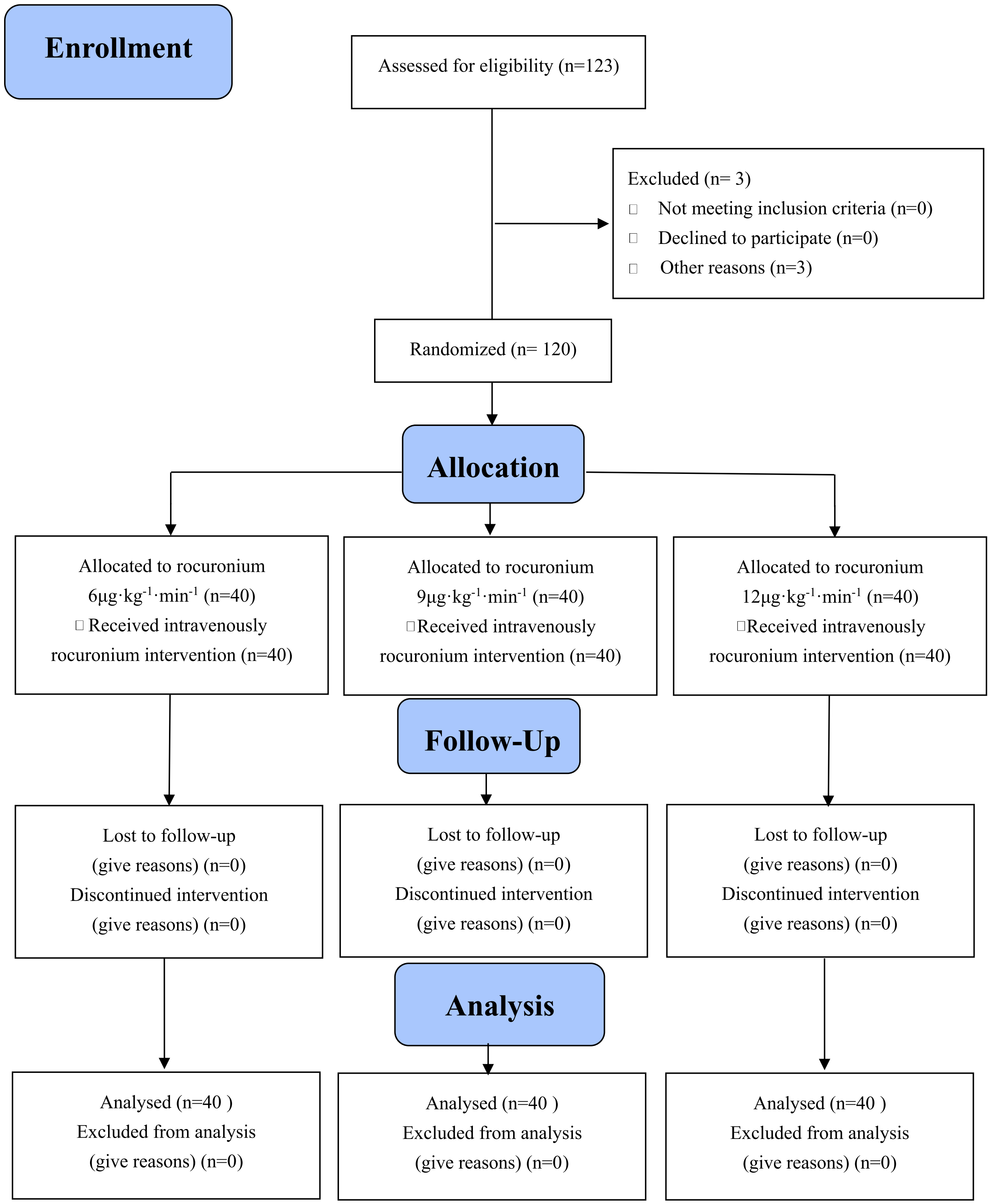

FIGURE 1 Patient enrollment and allocation to groups A (rocuronium bromide 6 μg·kg-1·min-1), B (rocuronium bromide 9 μg·kg-1·min-1), and C (rocuronium bromide 12 μg·kg-1·min-1).

TABLE 1 Patient's demographic variables

	Group A ($n = 40$)	Group B ($n = 40$)	Group C ($n = 40$)	p Value
Age(years)	51.5 (45–58)	54.5 (47–58.8)	52.5 (49–57)	0.752[a]
Sex				
Male	22	21	23	0.904[b]
Female	18	19	17	
Weight(kg)	68.5 (60–75)	66 (60–75)	67 (60–72)	0.540[a]
Height(cm)	170 (160.5–176)	168 (162–176)	169(160–176)	0.807[a]
BMI(kg/m^2)	23.9 (23.3–24.4)	23.9 (22.5–24.4)	23.3 (22.6–24.3)	0.297[a]
ASA				
I	13	9	10	0.575[b]
II	27	31	30	

Note: Group A:rocuronium bromide was pumped at a dose of 6μg·kg^{-1}·min^{-1} during maintenance of muscle relaxation. Group B: 9μg·kg^{-1}·min^{-1}. Group C: 12μg·kg^{-1}·min^{-1};

ASA, American society of anaesthesiologists classification.

BMI, body mass index.

Shapiro-Wilk test employed for a test of the normality assumption.

[a]*p* values derived from Kruskal-Wallis H(K) test.

[b]*p* values derived from the chi-square test.

by the 2017 edition of Chinese Guidelines on Anesthesiology and Expert Consensus; despite the recommendation, its effect on neurophysiological monitoring and whether it meets operational requirements have been unknown.

Ideal muscle relaxation should meet the operational requirements, avoid interference with surgical operations and allow MEP monitoring. Some studies have shown that partial neuromuscular blockade can provide the right monitoring conditions for neurophysiological monitoring and improve the safety of anaesthesia and surgery.[11,12] Although the existing research results have shown the relationship between the degree of muscle relaxation and MEP amplitudes, most of the clinical anaesthesia in China does not have the requirement of monitoring the degree of muscle relaxation. Therefore, the purpose of this study was to identify an optimal muscle relaxant dose to provide useful reference information for spinal surgery.[16] We excluded patients who were anaesthetized for more than 30 min when the baseline potentials were recorded to keep the degree of muscle relaxation consistent between groups. However, some perioperative variables can influence SEPs, including anaesthesia, hypotension, hypothermia and depth of anaesthesia.[17-19] We kept the mean arterial blood pressure at 70–90 mmHg, core temperature at 36.5–37.3°C and BIS value at 40–60 so that the depth of anaesthesia was unlikely to cause differences in SEPs.

The completion of internal pedicle screw placement and spinal canal decompression is critical time points for SEPs and MEPs. To minimize the impact of surgery on the amplitudes of IONM, we recorded SEPs and MEPs immediately before pedicle screw fixation and immediately before spinal canal decompression. Although there was no motor defect before surgery in any patient, to exclude the effects of difference in motor conductivity of the four limbs in each individual, we focused on the amplitude differences within the group in this study.

A second concern related to the use of these three rocuronium dosages is whether any of these dosages of rocuronium could provide satisfactory muscle relaxation and avoid adverse consequences during spinal surgery. In the current investigation, six patients had unexpected body movements during the operation and one patient in group A (rocuronium 6.0 μg·kg^{-1}·min^{-1}) had spontaneous breathing recovery, which affected the operation process. Even worse, this patient experienced a serious bite injury with visible bleeding from deep lacerations of the tongue and the lip, requiring sutures. However, none of the patients in doses of 9.0 μg·kg^{-1}·min^{-1} or 12.0 μg·kg^{-1}·min^{-1} had unexpected body movement. Although the amplitude of SEPs in the three groups of patients was not affected by the rocuronium bromide dosage, the amplitude of MEPs decreased as the dose of rocuronium bromide increased. In particular, at a rocuronium bromide dose of 12.0 μg·kg^{-1}·min^{-1}, the MEPs were most significantly suppressed, which may affect the safety of the surgery. Based on these considerations, we conclude that the dose of rocuronium 9.0 μg·kg^{-1}·min^{-1} can not only provide excellent muscle relaxation but also produce no related side effects, and that this dose can be safely applied in this kind of surgery.

This study still has the following deficiencies. First, although this study selected the time points that would have a minimal impact on IONM parameters, the influence of surgery on the MEP amplitude of IONM was still unavoidable. Second, although this study employed total intravenous anaesthesia, which has a minimum impact on neurophysiological monitoring, the application of sedatives in anaesthesia might still affect IONM. Another potential shortcoming of this study was that the anaesthesiologists could not be blinded, as they needed to adjust drug

TABLE 2 Comparisons of SEP and MEP variables among the three groups

Groups	SEPs/MEPs	Time points	Left upper limb (μV)	Right upper limb (μV)	Left lower limb (μV)	Right lower limb (μV)
Group A *n* = 40	SEPs	T_1	2.41 (1.7–3.3)	2.5 (1.6–3.7)	1.87 (1.31–2.9)	2.15 (1.33–3.05)
		T_2	2.5 (1.5–3.1)	2.5 (1.73–3.7)	2.23 (1.39–3.18)	2.35 (1.6–2.88)
		T_3	2.7 (1.5–3.7)	2.4 (1.35–4.1)	2.3 (1.41–3.1)	2.1 (1.4–3.1)
		p-Value	0.119	0.362	0.678	0.282
	MEPs	T_1	234.7 (133.7–432.7)	256.8 (126.8–567.5)	144.65 (32.4–277.58)	112.55 (40.78–234.1)
		T_2	321.2 (133.7–580.3)	319.8 (189.6–577.6)	156.35 (53.25–268.83)	123.2 (47.15–243.6)
		T_3	277.8 (165.4–543.7)	326.7 (162.3–615.9)	154.7 (46.58–265.6)	127.75 (62.83–257.65)
		p-Value	0.249	0.123	0.523	0.294
Group B *n* = 40	SEPs	T_1	2.5 (1.8–3.5)	2.93 (1.7–3.7)	1.75 (1.2–3.10)	1.7 (1.32–2.77)
		T_2	2.7 (1.9–3.5)	2.8 (1.78–3.4)	1.73 (1.24–3.0)	1.85 (1.26–2.95)
		T_3	2.6 (1.8–3.5)	2.6 (1.7–3.5)	1.7 (1.4–3.1)	1.95 (1.43–2.61)
		p-Value	0.477	0.232	0.054	0.901
	MEPs	T_1	332.6 (131.1–562.3)	322.5 (112.5–621.3)	125.2 (47.58–251.33)	150.3 (61.65–326.58)
		T_2	332.1 (113.5–579.7)	321.5 (123.4–600.7)	139.7 (20.2–311.45)	162.35 (55.03–316.8)
		T_3	332.8 (132.6–562.3)	256.2 (133.9–543.2)	115.05 (50.93–253.48)	117.75 (38.03–326.55)
		p-Value	0.615	0.347	0.799	0.294
Group C *n* = 40	SEPs	T_1	2.3 (1.34–3.2)	2.43 (1.35–2.9)	1.9 (1.07–3.25)	2.1 (1.06–3.08)
		T_2	2.24 (1.48–3.13)	2.35 (1.69–3.13)	2.15 (1.13–3.08)	1.9 (0.81–3.18)
		T_3	2.22 (1.31–3.28)	2.5 (1.55–3.1)	2.29 (1.39–3.1)	2.0 (0.92–3.2)
		p-Value	0.942	0.264	0.397	0.795
	MEPs	T_1	473.2 (166.43–638.75)[b]	541.7 (179.83–676.4)[b]	188.75 (45.13–445.58)	187.8(73.83–485.45)[b]
		T_2	294.95 (132.58–589.98)[a]	385.15 (158.23–459.15)[a]	155.65 (5.53–426.58)	139.15 (19.8–423.05)[a]
		T_3	211.4 (114.65–499.2)[a]	276.25 (67.28–457.85)[ab]	53.3 (5.15–369.5)[ab]	143.4 (10.58–427.4)[a]
		p Value[c]	0.048	0.002	0.025	<0.001

Note: Group A:rocuronium bromide was pumped at a dose of 6 $\mu g\cdot kg^{-1}\cdot min^{-1}$ during maintenance of muscle relaxation. Group B: 9 $\mu g\cdot kg^{-1}\cdot min^{-1}$. Group C: 12 $\mu g\cdot kg^{-1}\cdot min^{-1}$;

T_1: the anaesthesia time of the basic potential.T_2: the anaesthesia time before pedicle screw placement.T_3: the anaesthesia time before spinal canal decompression. SEP, somatosensory evoked potential, MEP, motor evoked potential.

Shapiro-Wilk test was employed for test of normality assumption.

[a]$p<0.05$ vs.T_1, [b]$p < 0.05$ vs.T_2 (Wilcoxon test).

[c]*p* values were derived from Kruskal-Wallis H (K) test.

TABLE 3 Comparisons of the TOF count

	Group A	Group B	Group C	*p* Values
Incidence of unexpected movement				
Yes	6	0	0	0.026[a]
No	34	40	40	
Incidence of spontaneous breathing recovery				
Yes	1	0	0	0.5[a]
No	39	40	40	
TOF count				
T_1	0 (0–0)	0 (0–0)	0 (0–0.75)	0.955[b]
T_2	3 (2–3)#	2 (2–2)*	0 (0–0)*#	<0.001[b]
T_3	4 (4–4)#	2 (2–2)*	0 (0–0)*#	<0.001[b]

Note: TOF, train-of-four.
T_1: the anaesthesia time when the basic potential was obtained.
T_2: the anaesthesia time before pedicle screw placement.
T_3: the anaesthesia time before spinal canal decompression.
$^*p < 0.05$ vs. Group A, $^\#p < 0.05$ vs. Group B (Mann-Whitney U test).
Shapiro-Wilk test was employed for test of normality assumption.
[a]*p* values were derived from Fisher exact test.
[b]*p* values were derived from Kruskal-Wallis H(K) test.

TABLE 4 Perioperative clinical data

	Group A ($n = 40$)	Group B ($n = 40$)	Group C ($n = 40$)	*p* Value
Anaesthesia time (min)	200 (190–205)	200 (195–205.75)	200 (190–204)	0.536[a]
Operation time (min)	165 (155.75–170)	165 (160–170)	165 (155–170)	0.650[a]
T_1 (min)	25 (24–25)	25 (22.25–27)	25 (22.25–27)	0.220[a]
T_2 (min)	65 (60.5–67)	65 (63–67)	65 (63–67)	0.280[a]
T_3 (min)	118.50 ± 11.82	122.48 ± 9.02	123.05 ± 9.86	0.103[b]

Note: T_1: the anaesthesia time when the basic potential was obtained.
T_2: the anaesthesia time before pedicle screw placement.
T_3: the anaesthesia time before spinal canal decompression.
Shapiro-Wilk test was employed for test of normality assumption.
[a]*p* values were derived from Kruskal-Wallis H (K) test.
[b]*p* value was derived from single factor analysis of variance test.

administration and maintain the appropriate anaesthetic requirements for the patient during surgery. However, the intraoperative neurophysiology technologists who performed and recorded the MEP amplitudes and onset latencies were blinded to the type and doses of rocuronium used.

4 | WHAT IS NEW AND CONCLUSION

Rocuronium bromide at a rate of 9.0 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$ provided suitable and adequate muscle relaxation but did not inhibit IONM. Therefore, we conclude that this dose should be recommended for spinal surgery.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Patient consent statement: Written informed consent was obtained from all subjects participating in the trial.

Statement: The manuscript was prepared according to CONSORT checklists.

ETHICS APPROVAL STATEMENT

This study was approved by the Medical Ethics Committee of Second Affiliated Hospital of Harbin Medical University.

DATA AVAILABILITY STATEMENT

Some or all data, models, or code generated or used during the study are available from the corresponding author by request.

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