

# Ciprofol vs Propofol for Intraoperative Neurophysiological Monitoring in Elderly Patients Undergoing Spinal Surgery: A Randomized Controlled Trial

Gaofeng Fan<sup>1,2,\*</sup>, Zhenzhen Hu<sup>1,\*</sup>, Suyue Zheng<sup>3,\*</sup>, Shibiao Chen<sup>1</sup>, Kun Yi<sup>1</sup>, Shiping Yin<sup>1</sup>, Wenjie Sun<sup>1</sup>

<sup>1</sup>Department of Anesthesiology, the First Affiliated Hospital, Jiangxi Medica College, Nanchang University, Nanchang, Jiangxi, People's Republic of China; <sup>2</sup>Department of Anesthesiology, the Second Affiliated Hospital, Jiangxi Medica College, Nanchang University, Nanchang, Jiangxi, People's Republic of China; <sup>3</sup>Department of Neurosurgery, the First Affiliated Hospital, Jiangxi Medica College, Nanchang University, Nanchang, Jiangxi, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Wenjie Sun, Department of Anesthesiology, the First Affiliated Hospital, Jiangxi Medica College, Nanchang University, Nanchang, Jiangxi, People's Republic of China, Email ndyfy06740@ncu.edu.cn

**Purpose:** This study aimed to compare the effects of ciprofol and propofol on motor evoked potentials (MEPs) and somatosensory evoked potentials (SEPs) in elderly patients undergoing spinal surgery.

**Patients and Methods:** This trial enrolled 60 elderly patients scheduled for elective spinal surgery with intraoperative neurophysiological monitoring (IONM) and assigned them to Group C (receiving ciprofol) or Group P (receiving propofol) using random allocation. Primary outcome measures focused on MEPs and SEPs amplitudes of lower extremities at T6. The secondary outcomes encompassed neurophysiological measures (MEPs and SEPs latencies at T6, as well as their amplitudes and latencies at T5), hemodynamic parameters of heart rate (HR), mean arterial pressure (MAP), and bispectral index (BIS) values at T1-T6, along with the incidence of hypotension, bradycardia, requirements for vasoactive medications.

**Results:** Neurophysiological recordings at T6 showed significantly higher amplitudes in Group C across all measured parameters during inter-group comparison. For MEPs, Group C demonstrated greater amplitudes in lower extremities (1378  $\mu$ V, IQR 1256–1605 vs 1121  $\mu$ V, IQR 1077–1307;  $P < 0.001$ ). Similarly, SEPs were significantly elevated in Group C for lower extremities (1.34  $\mu$ V, IQR 0.9–1.63 vs 1.11  $\mu$ V, IQR 0.82–1.16;  $P = 0.013$ ). However, no inter-group differences existed in MEPs or SEPs latency. From T3 to T6, Group C exhibited higher MAP values than in Group P (all  $P < 0.05$ ); and no intergroup difference in BIS values was observed at T5-T6 (T5:  $47.4 \pm 4.0$  vs  $49.1 \pm 4.7$ ,  $P = 0.145$ ; T6:  $46.4 \pm 3.5$  vs  $46.2 \pm 4.0$ ,  $P = 0.892$ ). Group C had a reduced need for vasoactive medications (13% vs 50%,  $P = 0.002$ ), less hypotension incidence (17% vs 40%,  $P = 0.045$ ).

**Conclusion:** Ciprofol outperforms propofol in hemodynamic stability for the elderly undergoing spinal surgery, with less suppression of the amplitudes of MEPs and SEPs, and no prolongation of latency, thereby potentially improving the quality of IONM.

**Trial Registration Clinicaltrials.gov Identifier:** ChiCTR2400091429.

**Keywords:** ciprofol, propofol, spinal surgery, neurophysiologic monitoring, elderly patients

## Introduction

Intraoperative neurophysiologic monitoring (IONM) is a critical tool for a continuous assessment of spinal cord and neural integrity in anesthetized patients,<sup>1</sup> potentially reducing the risk of iatrogenic neurologic injury.<sup>2</sup> In spine surgery, motor evoked potentials (MEPs) and somatosensory evoked potentials (SEPs) stand out as the most widely utilized IONM techniques.<sup>3</sup> Analysis on SEPs enables the evaluation of sensory pathway integrity, while that of MEPs offers

insights into the motor pathways.<sup>4</sup> Monitoring MEPs and SEPs concurrently may guarantee a precise detection of impairments in both sensory and motor pathways.<sup>5</sup> In the current aging context, there is a rise in the number of the elderly undergoing spine surgery.<sup>6</sup> These patients often present with physiological decline and multiple comorbidities, including hypertension, coronary artery disease, and diabetes mellitus.<sup>7–9</sup> Moreover, owing to their diminished vascular autoregulation, elderly patients are susceptible to intraoperative blood pressure fluctuations and hypotension, and exhibit reduced tolerance to hypotension.<sup>10</sup>

It is well documented that both MEPs and SEPs may undergo a certain degree of changes with the use of different agents produce. For instance, muscle relaxants may inhibit MEPs,<sup>11</sup> and inhalation anesthetics can suppress the signals of SEPs and MEPs in a dose-dependent fashion.<sup>12,13</sup> In the clinical setting, total intravenous anesthesia (TIVA) with propofol and opioids is commonly adopted for individuals undergoing spinal surgeries requiring IONM.<sup>14</sup> Nonetheless, propofol may be a suboptimal option for the elderly owing to its notable cardiovascular side effects, such as bradycardia and hypotension.<sup>15</sup> Ciprofol is a novel sedative, given intravenously, which is derived from the structural framework of propofol.<sup>16</sup> It exhibits a binding affinity to Gamma-Aminobutyric Acid Type A (GABAA) receptors, approximately 4–5 times greater than that of propofol, suggesting enhanced receptor selectivity. Based upon this feature, it allows ciprofol to produce equivalent anesthetic effects at lower doses.<sup>16</sup> Therefore, ciprofol may be particularly well-suited for anesthesia in elderly patients as they typically require reduced anesthetic doses due to declining organ function and reserve.<sup>17</sup> Prior studies have confirmed the use of ciprofol for inducing and maintaining anesthesia, with confirmed safety and efficacy.<sup>18–22</sup> However, there is a lack of clinical trials investigating the use of ciprofol in surgeries involving IONM, making it a pertinent area of research to determine its impact on MEPs and SEPs. Accordingly, this study was scheduled to clarify their effects on MEPs and SEPs in our studied population.

## Materials and Methods

### Trial Design and Participants

This double-blind, randomized, interventional study compared the effects of ciprofol and propofol on MEPs and SEPs in elderly patients undergoing spinal surgery. We enrolled 60 patients over 60 years of age classified as American Society of Anesthesiologists (ASA) grade II–III, scheduled for elective spinal surgery with IONM. The study established Group C and Group P to respectively receive ciprofol and propofol following a random grouping principle. This study was approved by the Ethics Committee of The First Affiliated Hospital of Nanchang University, Jiangxi, China, under approval number (IIT [2023]324). Additionally, the trial was registered with the Chinese Clinical Trials Registry ([www.chictr.org.cn](http://www.chictr.org.cn); Registration number: ChiCTR2400091429). Written informed consent was obtained from all participants prior to enrollment.

This study included patients aged  $\geq 60$  years classified as ASA II–III undergoing elective spinal surgery with IONM, with the following exclusion criteria: (1) hypersensitivity to ciprofol, propofol or soy products; (2) cranial defects or implanted pacemakers; (3) severe hepatic or renal dysfunction; (4) pre-existing neuropsychiatric disorders (including but not limited to Alzheimer's disease, stroke, traumatic brain injury, intracranial hemorrhage or space-occupying lesions); (5) chronic use of sedatives/antidepressants; (6) history of alcohol abuse; (7) inability to provide informed consent or comply with study protocol.

### Interventions

All patients were routinely monitored in the aspects of pulse oximetry, electrocardiogram, non-invasive blood pressure measurement and Bispectral index (BIS) intraoperatively. Patients were subjected to anesthesia induction through intravenous administration of either 1.5–2 mg/kg propofol (Sichuan Kelun) (classified as Group P) or 0.3–0.4 mg/kg ciprofol (Liaoning Haisco) (named as Group C), supplemented with 0.4  $\mu\text{g}/\text{kg}$  sufentanil (Yichang Renfu) (0.4  $\mu\text{g}/\text{kg}$ ) and 0.2 mg/kg cis-atracurium (Hangzhou Ausia). Anesthesia maintenance was achieved through continuous infusion of propofol (4–8  $\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ) in Group P or ciprofol (1.0–1.5  $\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ) in Group C, combined with remifentanil (Yichang Renfu) (6–12  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ) and cis-atracurium (0.1  $\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ , discontinued upon initiating skin incision).

Following anesthesia induction, a radial artery cannulation was conducted for invasive monitoring of arterial blood pressure. Maintenance of the depth of anesthesia was determined by referring to BIS (40–60), with an end-tidal carbon dioxide maintained between 35 and 45 mmHg in the process of mechanical ventilation. All anesthetic agents were discontinued immediately following skin closure by the surgical team.

## Monitoring Methods for MEPs and SEPs

Via NIM-ECLIPSE system (Medtronic, Inc, Minnesota, USA), patients' MEPs and SEPs were monitored, with the placement of electrode following the modified 10–20 system as per the International League for Neurophysiology's Standard Guidelines for Scalp Electroencephalography Electrode Placement (2017).<sup>23</sup> The alarm threshold was defined as either: (1) >50% reduction in waveform amplitude relative to the baseline, or (2) >10% prolongation of latency relative to the baseline.<sup>24</sup> Baseline values were used for real-time clinical decision-making but are not available for quantitative comparative analysis. For monitoring MEPs, transcranial electrical stimulation was delivered through spiral electrodes positioned over the C3 and C4 regions using a multipulse train technique (6 pulses per train). Compound muscle action potentials were recorded via needle electrodes inserted into the thenar muscles of the upper extremities and either the tibialis anterior or extensor digitorum brevis muscles of the lower extremities. Standard stimulation parameters included intensity (100–300 V), pulse duration (0.2 ms), and interpulse interval (2 ms). Furthermore, SEPs were elicited through continuous electrical stimulation of peripheral nerves. Surface electrodes were positioned at the wrist (median and ulnar nerves) and ankle (posterior tibial nerve), with the distal electrode serving as the anode and proximal electrode as the cathode; while recording electrodes were placed at Cz and C3'/C4' for lower and upper extremity monitoring, respectively. Stimulation parameters were maintained at an intensity of 15–30 mA, interstimulus interval of 100–300 ms, and frequency of 3–5 Hz.

## Outcomes

Data collection was completed by trained research personnel at predetermined time points: T1 (Baseline measurements approximately 10 minutes before anesthesia induction), T2 (immediately following successful endotracheal intubation), T3 (after positioning the patient in the prone position), T4 (when making skin incision initially), T5 (50 minutes after the cessation of cis-atracurium), and T6 (completion of critical surgical phase).

Primary outcome measures focused on MEPs and SEPs amplitudes of lower extremities at T6. The secondary outcomes encompassed neurophysiological measures (MEPs and SEPs latencies at T6, as well as their amplitudes and latencies at T5), continuous monitoring of hemodynamic parameters [heart rate (HR), mean arterial pressure (MAP)], and BIS values at the above predetermined intraoperative time points, along with incidence of hypotension (MAP decreased by > 30% from baseline or MAP < 65 mmHg), bradycardia (HR < 50 bpm), and injection pain, as well as requirements for vasoactive medications, total administered doses of ciprofol or propofol, total volume of intravenous fluids administered, estimated blood loss, and urine output. For the determination of recovery, this study also took into consideration of the time to emergence, extubation, and achievement of Aldrete recovery score  $\geq 9$  points.

## Randomization

Participants were randomly assigned to either Group C or Group P in a 1:1 ratio using a computer-generated randomization sequence. To ensure allocation concealment, an independent researcher blinded to the study design or implementation was responsible for group assignment preparations. Considering the nature of the interventions, the attending anesthesiologists and neurophysiology monitoring team were necessarily aware of the group assignments, but with blinding for participants, surgical teams, outcome assessors, and data analysts throughout the study period.

## Statistical Analysis

After assessing data normality and homogeneity routinely, continuous variables were respectively presented as mean  $\pm$  standard deviation ( $M \pm SD$ ) (for normally) and median with interquartile range (IQR) (for non-normally). Between-group comparisons of continuous variables were conducted using independent samples *t*-tests or Mann–Whitney *U*-tests, as appropriate. Categorical variables [number (%)] were analyzed using chi-square tests. Within-group comparisons across

multiple time points were performed using repeated-measures analysis of variance. All data were analyzed in SPSS 27.0, with statistical difference determined when  $P < 0.05$ .

## Sample Size and Power Calculation

Based on preliminary data obtained from 30 patients (15 per group)—including median MEPs amplitudes in the lower extremities at T6 of 1324  $\mu\text{V}$  (IQR 1235–1421) in Group C and 1109  $\mu\text{V}$  (IQR 1036–1329) in Group P, as well as median SEPs amplitudes of 1.28  $\mu\text{V}$  (IQR 0.79–1.75) in Group C and 0.96  $\mu\text{V}$  (IQR 0.60–1.08) in Group P, we calculated, using PASS (NCSS LLC, Kaysville, UT, USA), that 27 patients per group would be required to achieve 90% power at a two-sided alpha level of 0.05. Finally, given a potential 10% dropout rate, 30 patients were enrolled in each group. The dataset used for the sample size calculation is provided in the [Supplementary Datasets 1](#).

## Results

During the study period from December 2024 and April 2025, 65 elderly patients were enrolled, with 60 patients ultimately included in the final analysis, with 30 cases each in Groups C and P ([Figure 1](#)).

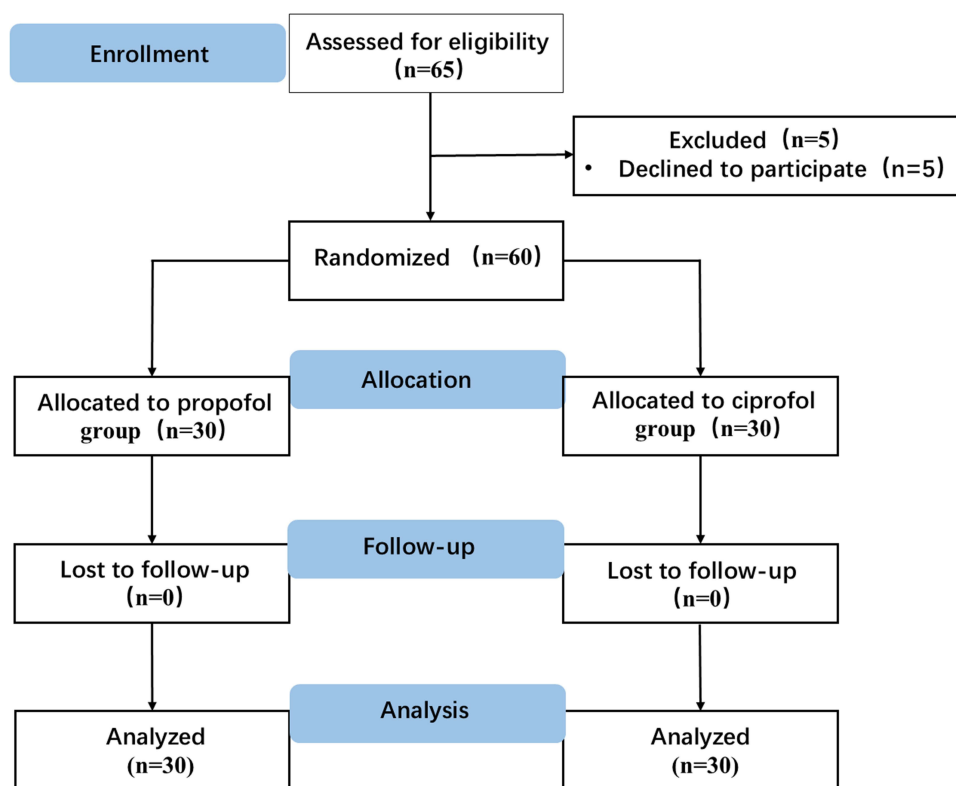
### Patient Characteristics

Both Group C and Group P shared similarity in gender, age, body mass index, ASA classification, comorbidities, surgical site and other baseline data, revealing no apparent inter-group differences ([Table 1](#)).

### Primary Outcomes

MEPs and SEPs in both upper and lower extremities were successfully elicited in all patients, and all surgeries were completed without complications.

Neurophysiological recordings at T6 showed significantly higher amplitudes in Group C across all measured parameters during inter-group comparison. For MEPs, Group C demonstrated greater amplitudes in both lower



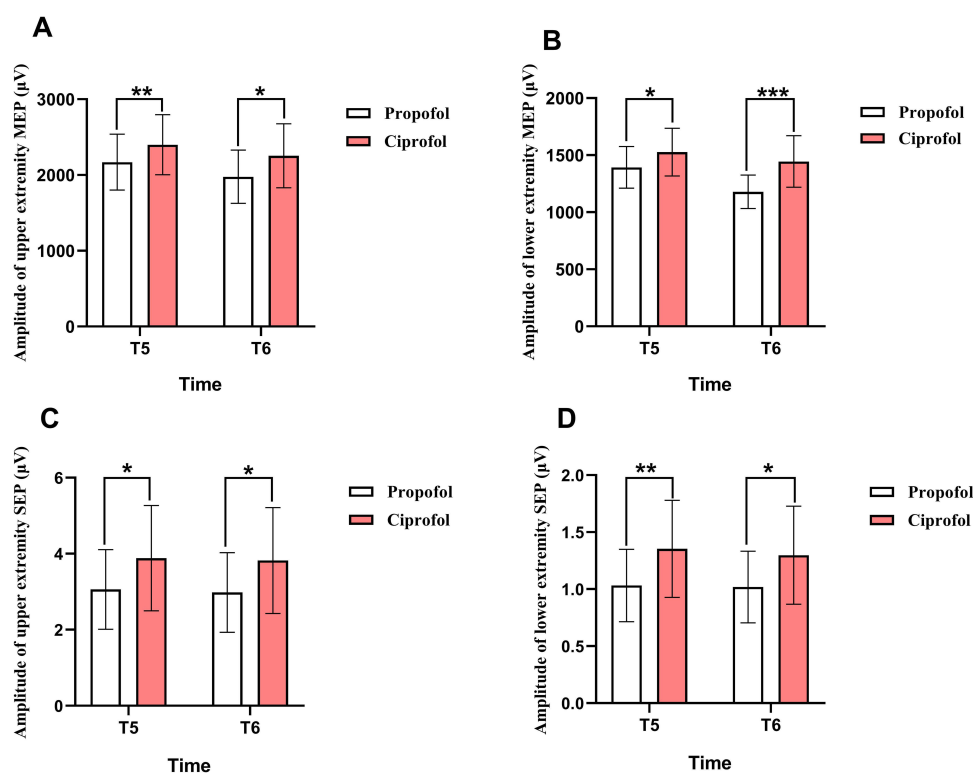
**Figure 1** CONSORT diagram.

**Table 1** Patient Characteristics

Variables	Propofol (n=30)	Ciprofol (n=30)	P-value
Age (years)	67.1±4.5	68.4±5.2	0.294
Sex (male/female, n)	12/18	13/17	0.793
BMI (kg/m <sup>2</sup> )	20.9±1.4	21.4±1.5	0.206
ASA class, n (%)			0.767
II	8 (27%)	7 (23%)	/
III	22 (73%)	23 (77%)	/
Cormobidities, n (%)			
Hypertension	12 (40%)	11 (37%)	0.791
Coronary artery disease	1 (3%)	2 (7%)	0.554
Diabetes	3 (10%)	5 (17%)	0.448
Surgical site, n (%)			
Cervical vertebra	17 (57%)	16 (53%)	0.795
Thoracic vertebra	8 (27%)	10 (33%)	0.513
Lumbar vertebra	5 (17%)	4 (13%)	0.718

**Notes:** Continuous variables were respectively presented as M ± SD, between-group comparisons were conducted using independent samples t-tests. Categorical variables [number (%)] were analyzed using chi-square tests. *P* < 0.05 There was a statistical difference between the two groups.

extremities (1378 μV, IQR 1256–1605 vs 1121 μV, IQR 1077–1307; *P* < 0.001) and upper extremities (2260 μV, IQR 1851–2589 vs 1894 μV, IQR 1756–2125; *P* = 0.011) (Figure 2A and B) (Table 2). Similarly, SEPs were significantly elevated in Group C for both lower extremities (1.34 μV, IQR 0.9–1.63 vs 1.11 μV, IQR 0.82–1.16; *P* = 0.013) and upper extremities (4.01 μV, IQR 2.42–5.33 vs 3.05 μV, IQR 2.18–3.88; *P* = 0.014) (Figure 2C and D) (Table 2).



**Figure 2** MEP and SEP amplitudes in lower and upper extremities across different time points. T5 (50 minutes after the cessation of cis-atracurium) and T6 (completion of critical surgical phase). (A) Amplitude of upper extremity MEP. (B) Amplitude of lower extremity MEP. (C) Amplitude of upper extremity SEP. (D) Amplitude of lower extremity SEP. *P* < 0.05 There was a statistical difference between the two groups. \**P* < 0.05, \*\**P* < 0.01, and \*\*\**P* < 0.001.

**Table 2** Amplitude and Latency of SEPs and MEPs at Different Time Points

Variables	Time	Propofol (n=30)	Cipropfol (n=30)	P-value
Amplitude of upper extremity SEPs ( $\mu$ V)	T5	3.12[2.28–4.11]	4.05[2.48–5.43]	0.021
	T6	3.05[2.18–3.88]	4.01[2.42–5.33]	0.014
Amplitude of lower extremity SEPs ( $\mu$ V)	T5	1.12[0.83–1.17]	1.36[0.95–1.70]	0.003
	T6	1.11[0.82–1.16]	1.34[0.90–1.63]	0.013
Amplitude of upper extremity MEPs ( $\mu$ V)	T5	2082[1922–2357]	2397[2081–2657]	0.009
	T6	1894[1756–2125]	2260[1851–2589]	0.011
Amplitude of lower extremity MEPs ( $\mu$ V)	T5	1351[1246–1505]	1498[1364–1698]	0.014
	T6	1121[1077–1307]	1378[1256–1605]	<0.001
Latency of upper extremity SEPs (ms)	T5	22.2[19.8–24.4]	21.1[19.3–23.6]	0.53
	T6	22.2[19.9–24.4]	21.2[19.3–23.5]	0.492
Latency of lower extremity SEPs (ms)	T5	39.6[35.2–42.4]	38.8[36.4–40.5]	0.482
	T6	39.8[35.0–42.5]	38.8[36.4–40.6]	0.52
Latency of upper extremity MEPs (ms)	T5	22.9[19.9–25.4]	22.2[20.3–24.4]	0.668
	T6	22.9[20.0–25.2]	22.3[20.3–24.3]	0.69
Latency of lower extremity MEPs (ms)	T5	38.8[36.7–40.9]	38.3[34.4–40.4]	0.258
	T6	38.8[36.7–41.1]	38.4[34.6–40.6]	0.318

**Notes:** T5 (50 minutes after the cessation of cis-atracurium) and T6 (completion of critical surgical phase). Continuous variables were respectively presented as median(IQR), between-group comparisons were conducted using Mann–Whitney U-tests.  $P < 0.05$  There was a statistical difference between the two groups.

**Table 3** HR, MAP and BIS at Different Time Points

Variables	Time	Propofol (n=30)	Cipropfol (n=30)	P-value
HR (bpm)	T1	83.0 $\pm$ 10.8	83.7 $\pm$ 13.3	0.840
	T2	60.0 $\pm$ 7.6	65.4 $\pm$ 7.0	0.005
	T3	64.7 $\pm$ 6.2	70.4 $\pm$ 7.0	0.001
	T4	63.6 $\pm$ 6.3	69.1 $\pm$ 7.7	0.003
	T5	62.8 $\pm$ 7.6	69.6 $\pm$ 5.7	<0.001
	T6	58.3 $\pm$ 6.3	65.9 $\pm$ 8.5	<0.001
MAP (mmHg)	T1	102.5 $\pm$ 8.7	103.1 $\pm$ 13.6	0.831
	T2	79.2 $\pm$ 10.9	84.3 $\pm$ 11.1	0.081
	T3	85.9 $\pm$ 10.3	92.9 $\pm$ 14.5	0.037
	T4	78.8 $\pm$ 10.8	85.9 $\pm$ 8.2	0.006
	T5	78.1 $\pm$ 8.4	84.8 $\pm$ 10.4	0.008
	T6	75.6 $\pm$ 7.5	81.7 $\pm$ 7.1	0.002
BIS	T1	95.1 $\pm$ 1.5	94.6 $\pm$ 1.5	0.155
	T2	39.7 $\pm$ 5.8	44.9 $\pm$ 3.3	<0.001
	T3	49.0 $\pm$ 5.4	46.4 $\pm$ 3.4	0.03
	T4	50.5 $\pm$ 4.6	47.1 $\pm$ 3.6	0.003
	T5	49.1 $\pm$ 4.7	47.4 $\pm$ 4.0	0.145
	T6	46.2 $\pm$ 4.0	46.4 $\pm$ 3.5	0.892

**Notes:** T1 (Baseline measurements approximately 10 minutes before anesthesia induction), T2 (immediately following successful endotracheal intubation), T3 (after positioning the patient in the prone position), T4 (when making skin incision initially), T5 (50 minutes after the cessation of cis-atracurium), and T6 (completion of critical surgical phase). Continuous variables were respectively presented as  $M \pm SD$ , between-group comparisons were conducted using independent samples t-tests.  $P < 0.05$  There was a statistical difference between the two groups.

## Secondary Outcomes

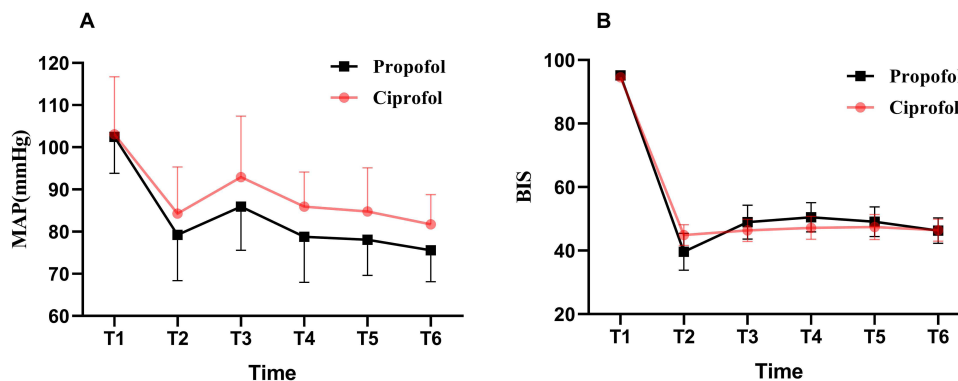
The secondary outcomes encompassed neurophysiological measures (MEPs and SEPs latencies at T6, as well as their amplitudes and latencies at T5). Group C had higher amplitudes of MEPs than Group P for both lower and upper extremities at T5 (1498  $\mu$ V, IQR 1364–1698 vs 1351  $\mu$ V, IQR 1246–1505;  $P=0.014$  and 2397  $\mu$ V, IQR 2081–2657 vs 2082  $\mu$ V, IQR 1922–2357;  $P=0.09$ ) (Figure 2A and B) (Table 2). However, no statistical inter-group differences were observed in the latency of MEPs at either T5 or T6 (all  $P > 0.05$ ) (Table 2). Similarly, Group C had much higher amplitudes of SEPs than Group P for both lower and upper extremities at T5 (1.36  $\mu$ V, IQR 0.95–1.70 vs 1.12  $\mu$ V, IQR 0.83–1.17;  $P=0.003$  and 4.05  $\mu$ V, IQR 2.48–5.43 vs 3.12  $\mu$ V, IQR 2.28–4.11;  $P=0.021$ ) (Figure 2C and D) (Table 2). In line with the MEPs findings, SEPs latency revealed no evident inter-group difference at T5 or T6 for either upper or lower extremities (all  $P > 0.05$ ) (Table 2).

HR analysis revealed comparable baseline values between groups at T1 ( $P=0.84$ ). However, from T2 to T6, Group C demonstrated significantly higher HR values compared to Group P ( $P = 0.005, 0.001, 0.003, <0.001, \text{ and } <0.001$ , respectively) (Table 3). Regarding MAP, no significant inter-group differences were observed at T1 ( $P=0.831$ ) or T2 ( $P=0.081$ ), However, from T3 to T6, Group C maintained markedly higher MAP values than Group P (92.9 $\pm$ 14.5 vs 85.9 $\pm$ 10.3, 85.9 $\pm$ 8.2 vs 78.8 $\pm$ 10.8, 84.8 $\pm$ 10.4 vs 78.1 $\pm$ 8.4, 81.7 $\pm$ 7.1 vs 75.6 $\pm$ 7.5; ( $P = 0.037, 0.006, 0.008, \text{ and } 0.002$ , respectively) (Table 3). Both groups exhibited parallel MAP trends across all time points (Figure 3A). As for BIS values, the group P showed marginally higher BIS values than the group C at T1 (94.6  $\pm$  1.5 vs 95.1  $\pm$  1.5,  $P = 0.155$ ). At T2, BIS values were significantly lower in group P than in group C (44.9  $\pm$  3.3 vs 39.7  $\pm$  5.8,  $P < 0.001$ ). From T3 to T5, BIS values remained consistently elevated in group P relative to the group C (T3: 46.4  $\pm$  3.4 vs 49.0  $\pm$  5.4,  $P = 0.03$ ; T4: 47.1  $\pm$  3.6 vs 50.5  $\pm$  4.6,  $P = 0.003$ ; T5: 47.4  $\pm$  4.0 vs 49.1  $\pm$  4.7,  $P = 0.145$ ). At T6, the final measurement time point, BIS values were comparable between the two groups (46.4  $\pm$  3.5 vs 46.2  $\pm$  4.0,  $P = 0.892$ ) (Table 3). Both anesthetic regimens maintained stable BIS trends during the maintenance period, with similar patterns of change observed between groups (Figure 3B).

Group C required significantly lower total doses of ciprofol/propofol (372  $\pm$  24 mg vs 1547  $\pm$  105 mg), but similar remifentanyl consumption to that of Group P (1566  $\pm$  121  $\mu$ g vs 1575  $\pm$  108  $\mu$ g,  $P=0.747$ ). Meanwhile, this group had reduced need for vasoactive medications (13% vs 50%,  $P = 0.002$ ), less hypotension incidence (17% vs 40%,  $P = 0.045$ ), and less injection pain (3% vs 30%,  $P=0.006$ ), but similar incidence of bradycardia (13% vs 20%,  $P=0.488$ ) (Table 4). The two groups demonstrated comparable baseline surgical characteristics (ie, operative duration, anesthesia time), as well as intraoperative fluid management (fluid intake, blood loss, and urine output), and recovery parameters (time to emergence, extubation, and achieving Aldrete score  $\geq 9$ ) (all  $P>0.05$ ) (Table 4).

## Discussion

IONM in spinal surgery can facilitate preferable neurological function in a real-time scene for patients under anesthesia, guiding surgical maneuvers and anesthetic adjustments to minimize iatrogenic neural injuries.<sup>3</sup> While enhancing surgical



**Figure 3** Time-course curves of MAP and BIS. T1 (Baseline measurements approximately 10 minutes before anesthesia induction), T2 (immediately following successful endotracheal intubation), T3 (after positioning the patient in the prone position), T4 (when making skin incision initially), T5 (50 minutes after the cessation of cis-atracurium), and T6 (completion of critical surgical phase). (A) The time course of MAP in both groups. (B) Time course of BIS in both groups.

**Table 4** Intraoperative Profiles and Postoperative Outcomes

Variables	Propofol (n=30)	Ciprofol (n=30)	P-value
Total amount of anesthetics			
Propofol or Ciprofol (mg)	1547.2±105.1	371.6±24.2	<0.001
Remifentanil (µg)	1575.2±108.3	1565.6±120.8	0.747
Intraoperative adverse events			
Injection pain, n (%)	9 (30%)	1 (3%)	0.006
Bradycardia, n (%)	6 (20%)	4 (13%)	0.488
Hypotension, n (%)	12 (40%)	5 (17%)	0.045
Need of vasoactive drugs, n (%)	15 (50%)	4 (13%)	0.002
Fluid intake and output			
Total infusion volume (mL)	2413.7±455.9	2303.3±422.6	0.335
Total blood loss (mL)	255.3±46.1	262.0±68.2	0.695
Total urine volume (mL)	508.3±213.8	513.3±104.8	0.909
Duration of different indicators			
Operation duration (min)	228±31.8	230.3±28.0	0.770
Anesthetic duration (min)	274.3±31.0	272.7±25.6	0.828
Awakening time (min)	30.5±6.6	29.5±4.2	0.472
Extubation time (min)	40.6±7.0	38.6±4.4	0.192
Time of Aldrete score ≥9 points (min)	60.1±6.7	58.7±4.6	0.348

**Notes:** Continuous variables were respectively presented as M ± SD, between-group comparisons were conducted using independent samples t-tests. Categorical variables [number (%)] were analyzed using chi-square tests. *P* <0.05 There was a statistical difference between the two groups.

safety, IONM reliability is vulnerable to multiple intraoperative factors, particularly anesthetic agents and hypotension, with additional interference from electrical artifacts, mechanical traction, and physiological fluctuations.<sup>25</sup> Indeed, both muscle relaxants and inhalational anesthetics are traditional options with effects of suppressing MEPs/SEPs signals. At present, propofol-remifentanil TIVA remains the standard anesthetic for IONM-assisted spine surgery, despite propofol's dose-dependent amplitude reduction of evoked potentials. This regimen often necessitates higher propofol doses to maintain optimal anesthesia depth, heightening the risk of hypotension in elderly patients particularly. As a novel intravenous anesthetic, ciprofol demonstrates reduced injection pain and improved hemodynamic stability compared to propofol.

There has been a well-established relationship between hemodynamic stability and evoked potential monitoring. Hypotension-induced ischemia in neural tissues can significantly compromise evoked potential recordings.<sup>26</sup> For example, 20% of patients undergoing pediatric spinal deformity surgery regained baseline evoked potential signals solely through blood pressure optimization (MAP increase from 68 to 86 mmHg).<sup>27</sup> Spinal cord perfusion, maintained through autoregulatory mechanisms, sustains vascular resistance and constant blood flow relying on adequate blood pressure.<sup>28</sup> However, age-related physiological changes and comorbidities (eg, hypertension and diabetes) may elevate the lower limit of autoregulation, necessitating higher perfusion pressures for adequate spinal cord oxygenation. Even with the absence of a clear definition of the optimal blood pressure threshold for spinal cord perfusion,<sup>29</sup> existing evidence suggests that MAP reductions below the autoregulatory threshold progressively diminish the amplitudes of MEPs and SEPs without affecting latency.<sup>30,31</sup> In our study, a fluid administration rate of approximately 600 mL/hour was used to maintain spinal cord perfusion pressure and minimize hemodynamic instability during complex spinal procedures. We found that patients receiving ciprofol maintained superior hemodynamic stability, with consistently higher MAP values throughout the anesthetic period compared to those given propofol. From T3 to T6, Group C maintained markedly higher MAP values than Group P (92.9 ± 14.5 vs 85.9 ± 10.3, 85.9 ± 8.2 vs 78.8 ± 10.8, 84.8 ± 10.4 vs 78.1 ± 8.4, 81.7 ± 7.1 vs 75.6 ± 7.5, *P* = 0.037, 0.006, 0.008, and 0.002, respectively) (Figure 3A) (Table 3), resulting in significantly lower rates of hypotension (17% vs 40%, *P* = 0.045) and reduced requirement for vasopressors

(13% vs 50%,  $P = 0.002$ ) (Table 4). Therefore, ciprofol may offer enhanced hemodynamic safety profile, and may better preserve cerebral and spinal cord perfusion in elderly patients, thereby creating more favorable conditions for IONM.

MEPs and SEPs demonstrate particular anesthetic sensitivity at three critical sites: motor cortex, spinal anterior horn cells, and neuromuscular junctions, supporting the pronounced effect of neuromuscular blockers on MEPs. Given higher synaptic density in cortical structures, cortical SEPs show greater anesthetic susceptibility than spinal responses.<sup>26</sup> A phenomenon corroborated by parallel EEG changes, both cortical SEPs and EEG exhibit dose-dependent suppression through shared synaptic mechanisms, with progressive inhibition at higher anesthetic concentrations.<sup>26,32</sup> In this study, patients were subjected to TIVA with either ciprofol or propofol in combination with remifentanyl for anesthesia maintenance. Regarding the comparison of anesthetic administration between the two groups, it is noteworthy that no significant difference was observed in the total consumption of remifentanyl ( $1566 \pm 121 \mu\text{g}$  vs  $1575 \pm 108 \mu\text{g}$ ,  $P=0.747$ ). However, the total dosage of ciprofol used in group C was only 0.24 times that of propofol in the group P ( $372 \pm 24 \text{ mg}$  vs  $1547 \pm 105 \text{ mg}$ ) (Table 4). This result can be explained by ciprofol's higher binding affinity to GABAA receptors, which enables comparable anesthetic efficacy at only 20–25% of the propofol dose.<sup>16</sup> The consistency between the ratio of total drug usage (0.24) and the previously reported difference in GABAA receptor binding affinity suggests that the difference in dosage is unlikely to have substantially influenced the amplitudes of MEPs and SEPs.

Therefore, anesthetic depth remains a critical consideration when interpreting the outcomes. At T1 (awake state), the BIS values was slightly higher in the group P ( $95.1 \pm 1.5$ ) than in group C ( $94.6 \pm 1.5$ ), although this difference was not statistically significant ( $P = 0.155$ ). By T2 (after successful intubation), BIS values were significantly lower in the group P ( $39.7 \pm 5.8$ ) compared to the group C ( $44.9 \pm 3.3$ ;  $P < 0.001$ ) (Table 3). This discrepancy may be attributed to injection pain associated with propofol, which can provoke discomfort or agitation during induction, occasionally necessitating supplemental anesthetic boluses and resulting in transient deepening of anesthesia. In contrast, ciprofol administration was associated with markedly reduced injection pain (3% vs 30%,  $P=0.006$ ) (Table 4). From T3 to T5, BIS values were consistently higher in group P (T3:  $49.0 \pm 5.4$  vs  $46.4 \pm 3.4$ ,  $P = 0.03$ ; T4:  $50.5 \pm 4.6$  vs  $47.1 \pm 3.6$ ,  $P = 0.003$ ; T5:  $49.1 \pm 4.7$  vs  $47.4 \pm 4.0$ ,  $P = 0.145$ ) (Table 3). Most importantly, at T6—the primary endpoint for neurophysiological assessment—BIS values were comparable between the two groups ( $46.4 \pm 3.5$  vs  $46.2 \pm 4.0$ ,  $P = 0.892$ ) (Table 3), indicating equivalent anesthetic depth at the time of key measurement. Furthermore, ciprofol maintained stable BIS values comparable to propofol throughout the maintenance period (Figure 3B).

The observed difference in MEPs amplitudes at T6 between the two groups may be explained by the “wearing-off” effect of anesthetics. Previous studies have indicated that prolonged infusion of propofol can lead to a gradual reduction in MEPs amplitudes, a phenomenon referred to as the “anesthetic fade” effect.<sup>33</sup> This effect tends to occur when the duration of anesthesia exceeds 235 minutes or the total dose of propofol exceeds 1550 mg. The underlying mechanism may involve the accumulation of high doses of propofol at synaptic junctions, which inhibits synaptic activity in the motor cortex and compromises the excitability transmission of anterior horn cells in the spinal cord, thereby suppressing MEPs amplitudes.<sup>34,35</sup> Our findings are consistent with this phenomenon. For instance, in group P, the MEPs amplitudes of lower extremities decreased at T6 compared to T5 ( $1121 [1077–1307] \mu\text{V}$  vs  $1351 [1246–1505] \mu\text{V}$ ). Similarly, a reduction was observed in group C ( $1378 [1256–1605] \mu\text{V}$  vs  $1498 [1364–1698] \mu\text{V}$ ) (Table 2). The mean duration of anesthesia in both groups exceeded 270 minutes ( $272.7 \pm 25.6 \text{ min}$  vs  $274.3 \pm 31.0 \text{ min}$ ) (Table 4), and the total propofol dose in group P reached 1575 mg. After excluding intraoperative neural injury and other potential causes of MEPs suppression, and considering the delayed drug metabolism and clearance in elderly patients, we speculate that a certain degree of anesthetic fade effect occurred in both groups. As discussed earlier, although the absolute doses of ciprofol and propofol differed, their dose-efficacy ratios were comparable, and anesthetic depth was equivalent at T6. It is reasonable to hypothesize that the lower total dose of ciprofol may have resulted in less accumulation at synaptic junctions compared to propofol during prolonged infusion, thereby attenuating the anesthetic fade effect in group C. However, this remains speculative, as no experimental studies have directly compared the extent of synaptic accumulation between these two agents under conditions of equivalent dose-efficacy ratios during long-term infusion.

Currently, propofol remains the preferred sedative for IONM due to its predictable effects at clinical concentrations.<sup>28</sup> However, our study demonstrated that ciprofol offers several distinct advantages: it caused no prolongation of MEPs or SEPs latencies, induced less amplitude suppression compared to propofol, and allowed effective monitoring of MEPs and

SEPs in elderly patients undergoing spinal surgery. Overall, ciprofol exhibited superior neurophysiological preservation relative to propofol.

## Study Limitations

It should be acknowledged that our study assessed neuromuscular blocking agent metabolism relied solely on pharmacokinetic modeling, lacking direct monitoring of drug concentrations or neuromuscular function. Second, the inherent complexity of IONM imposes potential challenge, despite our attempts to control for confounding variables. IONM outcomes may be compromised by numerous factors such as individual physiological variations and the dynamic nature of surgical procedures. This study, even with rigorous design, cannot entirely eliminate the potential impact of these confounding variables on our results.

## Conclusion

This study suggests preferable effects of ciprofol in reducing the suppression of MEPs and SEPs amplitudes in elderly patients undergoing spinal surgery, outperforming propofol, without prolonging latency, while maintaining optimal hemodynamic stability. Collectively, ciprofol may represent a superior alternative for both anesthesia induction and maintenance in this patient population.

## Abbreviations

IONM, Intraoperative Neurophysiologic Monitoring; MEPs, Motor Evoked Potentials; SEPs, Somatosensory Evoked Potentials; TIVA, Total Intravenous Anesthesia; GABAA, Gamma-Aminobutyric Acid Type A; ASA, American Society of Anesthesiologists; Group C, Ciprofol Group; Group P, Propofol Group; EEG, electrocardiogram; BIS, Bispectral index; HR, Heart Rate; MAP, Mean Arterial Pressure;  $M \pm SD$ , Mean  $\pm$  Standard Deviation; IQR, interquartile range.

## Data Sharing Statement

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and received approval from the Hospital Ethics Committee of the First Affiliated Hospital of Nanchang University, No. 7 Yongwai Zhengjie, Nanchang, Jiangxi Province, China. This study was registered with the China Clinical Trial Registry [www.chictr.org.cn](http://www.chictr.org.cn) (registration number: ChiCTR2400091429). Written informed consent was obtained from all volunteers before the start of study procedures.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

## References

- Scibilia A, Terranova C, Rizzo V, et al. Intraoperative neurophysiological mapping and monitoring in spinal tumor surgery: sirens or indispensable tools? *Neurosurgical Focus*. 2016;41(2):E18. doi:10.3171/2016.5.Focus16141
- Martin DP, Bhalla T, Thung A, et al. A preliminary study of volatile agents or total intravenous anesthesia for neurophysiological monitoring during posterior spinal fusion in adolescents with idiopathic scoliosis. *Spine*. 2014;39(22):E1318–24. doi:10.1097/brs.0000000000000550
- Pastorelli F, Di Silvestre M, Plasmati R, et al. The prevention of neural complications in the surgical treatment of scoliosis: the role of the neurophysiological intraoperative monitoring. *European Spine J*. 2011;20(Suppl S1):S105–14. doi:10.1007/s00586-011-1756-z
- Di Domenico M, Viola D, Izzo A, et al. Methods and principles of the intraoperative neurophysiologic monitoring in neurosurgery. *Acta Neurochirurgica Suppl*. 2023;135:45–49. doi:10.1007/978-3-031-36084-8\_9
- Charalampidis A, Jiang F, Wilson JRF, Badhiwala JH, Brodke DS, Fehlings MG. The use of intraoperative neurophysiological monitoring in spine surgery. *Global Spine J*. 2020;10(1\_suppl):104s–114s. doi:10.1177/2192568219859314
- Wang AY, Olmos M, Ahsan T, et al. Safety and feasibility of spinal anesthesia during simple and complex lumbar spine surgery in the extreme elderly ( $\geq 80$  years of age). *Clin Neurol Neurosurg*. 2022;219:107316. doi:10.1016/j.clineuro.2022.107316
- Steinmetz J, Rasmussen LS. The elderly and general anesthesia. *Minerva anesthesiologica*. 2010;76(9):745–752.
- Bettelli G. Preoperative evaluation of the elderly surgical patient and anesthesia challenges in the XXI century. *Aging Clin Experim Res*. 2018;30(3):229–235. doi:10.1007/s40520-018-0896-y
- Brallier JW, Deiner S. The elderly spine surgery patient: pre- and intraoperative management of drug therapy. *Drugs Aging*. 2015;32(8):601–609. doi:10.1007/s40266-015-0278-5
- Zhao B, Chen X, Chen Q, et al. Intraoperative hypotension and related risk factors for postoperative mortality after noncardiac surgery in elderly patients: a retrospective analysis report. *Clin Interventions Aging*. 2021;16:1757–1767. doi:10.2147/cia.S327311
- Nunes RR, Bersot CDA, Garritano JG. Intraoperative neurophysiological monitoring in neuroanesthesia. *Curr Opinion I Anaesthesiol*. 2018;31(5):532–538. doi:10.1097/aco.0000000000000645
- Chong CT, Manninen P, Sivanaser V, Subramanyam R, Lu N, Venkatraghavan L. Direct comparison of the effect of desflurane and sevoflurane on intraoperative motor-evoked potentials monitoring. *J Neurosurg Anesthesiol*. 2014;26(4):306–312. doi:10.1097/ana.0000000000000041
- Wilent WB, Tesdahl EA, Trott JT, et al. Impact of inhalational anesthetic agents on the baseline monitorability of motor evoked potentials during spine surgery: a review of 22,755 cervical and lumbar procedures. *Spine J*. 2021;21(11):1839–1846. doi:10.1016/j.spinee.2021.07.002
- Walker CT, Kim HJ, Park P, et al. Neuroanesthesia guidelines for optimizing transcranial motor evoked potential neuromonitoring during deformity and complex spinal surgery: a delphi consensus study. *Spine*. 2020;45(13):911–920. doi:10.1097/brs.00000000000003433
- Marik PE. Propofol: therapeutic indications and side-effects. *Curr Pharm Des*. 2004;10(29):3639–3649. doi:10.2174/1381612043382846
- Lu M, Liu J, Wu X, Zhang Z, Tokumine J. Ciprofol: a novel alternative to propofol in clinical intravenous anesthesia? *Biomed Res Int*. 2023;2023(1):7443226. doi:10.1155/2023/7443226
- Andres TM, McGrane T, McEvoy MD, Allen BFS. Geriatric Pharmacology: an Update. *Anesthesiology Clinics*. 2019;37(3):475–492. doi:10.1016/j.anclin.2019.04.007
- Liang P, Dai M, Wang X, et al. Efficacy and safety of ciprofol vs. propofol for the induction and maintenance of general anaesthesia: a multicentre, single-blind, randomised, parallel-group, Phase 3 clinical trial. *Euro J Anaesthesiol*. 2023;40(6):399–406. doi:10.1097/eja.0000000000001799
- Qin K, Qin W-Y, Ming S-P, Ma X-F, Du X-K. Effect of ciprofol on induction and maintenance of general anesthesia in patients undergoing kidney transplantation. *Eur Rev Med Pharmacol Sci*. 2022;26(14):5063–5071. doi:10.26355/eurrev\_202207\_29292
- Zeng Y, Wang DX, Lin ZM, et al. Efficacy and safety of HSK3486 for the induction and maintenance of general anesthesia in elective surgical patients: a multicenter, randomized, open-label, propofol-controlled Phase 2 clinical trial. *Euro Rev Med Pharmacol Sci*. 2022;26(4):1114–1124. doi:10.26355/eurrev\_202202\_28101
- Liu L, Wang K, Yang Y, et al. Population pharmacokinetic/pharmacodynamic modeling and exposure-response analysis of ciprofol in the induction and maintenance of general anesthesia in patients undergoing elective surgery: a prospective dose optimization study. *J Clin Anesthesia*. 2024;92:111317. doi:10.1016/j.jclinane.2023.111317
- Ding -Y-Y, Long Y-Q, Yang H-T, Zhuang K, Ji F-H, Peng K. Efficacy and safety of ciprofol for general anaesthesia induction in elderly patients undergoing major noncardiac surgery: a randomised controlled pilot trial. *Euro J Anaesthesiol*. 2022;39(12):960–963. doi:10.1097/eja.0000000000001759
- American Clinical Neurophysiology Society. Guideline 9D: guidelines on short-latency somatosensory evoked potentials. *J Clin Neurophys*. 2006;23(2):168–179. doi:10.1097/00004691-200604000-00013
- Liu Q, Wang Q, Liu H, Wu WKK, Chan MTV. Warning criteria for intraoperative neurophysiologic monitoring. *Curr Opinion I Anaesthesiol*. 2017;30(5):557–562. doi:10.1097/aco.0000000000000505
- Lotto ML, Banoub M, Schubert A. Effects of anesthetic agents and physiologic changes on intraoperative motor evoked potentials. *J Neurosurg Anesthesiol*. 2004;16(1):32–42. doi:10.1097/00008506-200401000-00008
- Sloan TB, Heyer EJ. Anesthesia for intraoperative neurophysiologic monitoring of the spinal cord. *J Clin Neurophys*. 2002;19(5):430–443. doi:10.1097/00004691-200210000-00006
- Yang J, Skaggs DL, Chan P, et al. Raising mean arterial pressure alone restores 20% of intraoperative neuromonitoring losses. *Spine*. 2018;43(13):890–894. doi:10.1097/brs.0000000000002461
- Sahinovic MM, Gadella MC, Shils J, Dulfer SE, Drost G. Anesthesia and intraoperative neurophysiological spinal cord monitoring. *Curr Opinion I Anaesthesiol*. 2021;34(5):590–596. doi:10.1097/aco.0000000000001044
- Dulfer SE, Sahinovic MM, Lange F, et al. The influence of depth of anesthesia and blood pressure on muscle recorded motor evoked potentials in spinal surgery. A prospective observational study protocol. *J Clin Monitor Comp*. 2021;35(5):967–977. doi:10.1007/s10877-020-00645-1
- Banoub M, Tetzlaff JE, Schubert A. Pharmacologic and physiologic influences affecting sensory evoked potentials: implications for perioperative monitoring. *Anesthesiology*. 2003;99(3):716–737. doi:10.1097/0000542-200309000-00029
- Fehlings MG, Tator CH, Linden RD. The relationships among the severity of spinal cord injury, motor and somatosensory evoked potentials and spinal cord blood flow. *Electroencephalograph Clin Neurophys*. 1989;74(4):241–259. doi:10.1016/0168-5597(89)90055-5
- Sloan TB. Anesthetic effects on electrophysiologic recordings. *J Clin Neurophys*. 1998;15(3):217–226. doi:10.1097/00004691-199805000-00005

33. Ushirozako H, Yoshida G, Hasegawa T, et al. Characteristics of false-positive alerts on transcranial motor evoked potential monitoring during pediatric scoliosis and adult spinal deformity surgery: an “anesthetic fade” phenomenon. *J Neurosurg Spine*. 2019;1–9. doi:10.3171/2019.9.Spine19814
34. Tanaka S, Watanabe T, Takanashi J, Oka H, Hashimoto R, Akimoto J. Effect of compound muscle action potential after peripheral nerve stimulation normalization on anesthetic fade of intraoperative transcranial motor-evoked potential. *J Clin Neurophys*. 2021;38(4):306–311. doi:10.1097/wnp.0000000000000692
35. Ushirozako H, Yoshida G, Kobayashi S, et al. Impact of total propofol dose during spinal surgery: anesthetic fade on transcranial motor evoked potentials. *J Neurosurg Spine*. 2019;8:1–9. doi:10.3171/2018.10.Spine18322

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