

Effects of depth of neuromuscular blockade on the BIS-guided propofol requirement

A randomized controlled trial

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Abstract

Background: Deep neuromuscular blockade is considered beneficial for improving the surgical space condition during laparoscopic surgery. Adequacy of the surgical space condition may affect the anesthetists' decision regarding titration of depth of anesthesia. We investigated whether deep neuromuscular blockade reduces the propofol requirement under bispectral index monitoring compared to moderate neuromuscular blockade.

Methods: Adult patients undergoing elective laparoscopic colorectal surgery were randomly allocated to a moderate or deep group. A train-of-four count of 1–2 in the moderate group, and a post-tetanic count of 1–2 in the deep group, were maintained by continuous infusion of rocuronium. The induction and maintenance of anesthesia were achieved by target-controlled infusion of propofol and remifentanyl. The dose of propofol was adjusted to maintain the bispectral index in the range of 40–50. The remifentanyl dose was titrated to maintain the systolic blood pressure to within 20% of the ward values.

Results: A total of 82 patients were included in the analyses. The mean±SD dose of propofol was 7.54 ± 1.66 and 7.42 ± 1.01 mg·kg⁻¹·h⁻¹ in the moderate and deep groups, respectively ($P = .104$). The mean±SD dose of remifentanyl was 4.84 ± 1.74 and 4.79 ± 1.77 μg kg⁻¹ h⁻¹ in the moderate and deep groups, respectively ($P = .688$). In comparison to the moderate group, the deep group showed significantly lower rates of intraoperative patient movement (42.9% vs 22.5%, respectively, $P = .050$) and additional neuromuscular blocking agent administration (76% vs 53%, respectively, $P = .007$). Postoperative complications, including pulmonary complications, wound problems and reoperation, were not different between the two groups.

Conclusion: Deep neuromuscular blockade did not reduce the bispectral index-guided propofol requirement compared to moderate neuromuscular blockade during laparoscopic colon surgery, despite reducing movement of the patient and the requirement for a rescue neuromuscular blocking agent.

Trial registration: Clinicaltrials.gov (NCT03890406)

Abbreviations: ANI = Analgesia nociception index, ASA = American Society of Anesthesiologists, BIS = Bispectral index, EEG = Electroencephalography, EMG = Electromyography, ETCO₂ = End-tidal carbon dioxide, GCRP = Good clinical research practice, NMB = Neuromuscular blockade, NMBA = Neuromuscular blocking agent, PACU = Post-anesthesia care unit, POD = Postoperative day, PTC = Post-tetanic count, TCI = Target-controlled infusion, TOF = Train-of-four.

Keywords: consciousness monitors, laparoscopy, neuromuscular blockade, propofol

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

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1. Introduction

Since the introduction of sugammadex, a number of studies have assessed the potential benefits of deep neuromuscular blockade (NMB). Among the various putative advantages, improvement of surgical space condition in laparoscopic surgery is the best-supported. Studies have indicated that, in comparison to moderate block, deep block facilitates higher surgical condition ratings score, enables lower pressure pneumoperitoneum and prevents inadvertent patient movement.^[1–7]

Previous studies comparing deep and moderate NMB reported that the surgical space condition was inadequate in a large proportion of patients.^[7,8] Anesthetists may tend to reduce the dose of anesthetics for deep NMB and may increase the dose for shallow to moderate NMB. When the surgical space condition is judged inadequate for surgery, it is essential to determine whether this is due to low anesthetic depth or insufficient muscle relaxation. These factors can only be assessed through proper monitoring, for example using the bispectral index (BIS) and a nerve stimulator to measure the depth of anesthesia and NMB, respectively. No studies have investigated the effect of deep NMB on the BIS-guided anesthetic requirement.

Excessive use of anesthetics is associated with a higher rate of adverse outcomes, including postoperative mortality.^[9–12] Several researchers have suggested that this is an epiphenomenon of other factors, such as age, comorbidities and hemodynamic instability.^[13,14] However, given the reports on neurotoxicity, cardiovascular depression, and proinflammatory and immunosuppressive effects of general anesthetic agents, we cannot exclude the possibility that adverse events are dose-dependent, and that minimising the dose of anesthetic agent could improve the outcome.^[9,15–20]

The present study investigated whether deep NMB reduces the BIS-guided propofol requirement during laparoscopic colorectal surgery, in comparison to moderate NMB.

2. Methods

2.1. Ethics

This prospective randomized controlled study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-1805-466-006, June 20, 2018), Gyeonggi-do, Republic of Korea (Chairperson: Prof. J. Lee), and was registered at Clinicaltrials.gov. (NCT03890406, March 25, 2019). Neuromuscular monitoring followed good clinical research practice (GCRP) guidelines for studies investigating NMB agents.^[21]

2.2. Study protocol

Patients aged 19–75 years scheduled for elective colorectal surgery for colorectal cancer at Seoul National University Bundang Hospital (SNUBH) from March 2019 to December 2019 were enrolled in this study. The exclusion criteria were an American Society of Anesthesiologists (ASA) physical status ≥ 3 , body mass index (BMI) < 18.5 or $\geq 35 \text{ kg m}^{-2}$, history of severe cardiopulmonary, renal or hepatic disease, pregnancy, history of hypersensitivity to anesthetic agents or NMB agents, history of malignant hyperthermia, medications known to affect neuromuscular function, and previous history of open major lower abdominal surgery. Written informed consent was obtained from all subjects.

Patients were randomly allocated to the moderate or deep group using computer-generated random numbers kept in sealed envelopes.

In the operating theatre, the patients were firstly premedicated with $0.03 \text{ mg}\cdot\text{kg}^{-1}$ of midazolam. After non-invasive blood pressure monitoring, 3-electrode electrocardiogram, pulse oximetry, and BIS (BIS Quattro; Medtronic, Minneapolis, MN) monitoring were started, followed by acceleromyography (TOF-WatchSX; Organon, Dublin, Ireland). Two surface electrodes were placed over the right ulnar nerve separated by a distance of 3–6 cm. The transducer was attached to the thumb and the other four fingers were immobilized.

For induction of anesthesia, target-controlled infusion (TCI) of propofol $4.0 \mu\text{g}\cdot\text{ml}^{-1}$ (Marsh model) and remifentanyl $3.0 \text{ ng}\cdot\text{ml}^{-1}$ (Minto model) was used. After the patient had lost consciousness, a 50-Hz tetanic stimulus was applied for 5 s. Following stabilisation and calibration of the acceleromyograph, rocuronium $0.6 \text{ mg}\cdot\text{kg}^{-1}$ was administered and tracheal intubation was performed after the loss of all train-of-four (TOF) responses. Anesthesia was maintained by TCI of propofol and remifentanyl, and continuous infusion of rocuronium. The

target concentration of propofol was adjusted in increments of $0.1 \mu\text{g}\cdot\text{ml}^{-1}$ to maintain a BIS of 40–50, while remifentanyl was adjusted in increments $0.1 \text{ ng}\cdot\text{ml}^{-1}$ to maintain systolic blood pressure within 20% of the ward values. The infusion of rocuronium was started at $0.6 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ and adjusted in increments of $0.1 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ to maintain a TOF count of 1–2 in the moderate group and a post-tetanic count (PTC) of 1–2 in the deep group. A rocuronium bolus dose of 5 mg was used for rapid titration of the level of NMB at the discretion of the attending anesthetist. Intraoperative patient movement, surgeon's request for additional neuromuscular blocking agent (NMBA), and actual bolus NMBA administration were documented. Patient movement included just a dimpling on the end-tidal carbon dioxide (ETCO₂) graph, even without any gross movement. When the patient moved or the surgeon requested additional NMBA, the current level of NMB was documented. If the level of NMB was out of range of the study group, the dose of rocuronium was adjusted. If it was within range of the study group, the dose of remifentanyl was adjusted.

At the end of surgery, the patients were given 2 or 4 mg kg⁻¹ sugammadex (Bridion; Merck Sharp and Dohme, Oss, The Netherlands) according to the NMB status, and extubated after confirmation of a TOF ratio ≥ 0.9 .

The doses of propofol and remifentanyl used, operating time, anesthesia time and post-anesthesia care unit (PACU) stay were also recorded. In addition, the length of postoperative hospital stay and postoperative complications, including respiratory complications, surgical site complications and reoperation within 30 days, were reviewed after discharge.

2.3. Statistical analyses

The primary outcome variable was the dose of propofol used during anesthesia. The secondary outcome variables were the dose of remifentanyl used, intraoperative patient movement, surgeon requests for additional NMBA, actual bolus NMBA administration and postoperative complications.

Based on a previous study, the mean \pm SD dose of propofol used during laparoscopic cholecystectomy with moderate block was $7.25 \pm 1.13 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$.¹ A sample size of 44 patients in each group was estimated to be required to detect a 20% difference between the groups with a 5% type 1 error rate, 80% power and 10% dropout rate.

The groups were compared using Student's *t* test or the Mann–Whitney *U* test for continuous variables, and by the χ^2 test or Fisher's exact test for non-continuous variables, using SPSS software for Windows (ver. 25.0; SPSS Inc., Chicago, IL, USA). In all analyses, $P < .05$ was taken to indicate statistical significance.

3. Results

A total of 88 patients were eligible for inclusion in the study. Neuromuscular monitoring had to be discontinued in three cases due to mechanical problems. Two other cases required temporary supplemental inhaled anesthetics to maintain anesthesia due to disruption of intravenous access, and one was converted to open surgery. Therefore, 82 patients were included in the analysis, of whom 4 were excluded from the postoperative outcomes analysis due to an error in administration of the reversal agent (Fig. 1).

Three surgeons (surgeons A–C) participated in the study. Estimated blood loss was minimal in the majority of the patients and no case required transfusion. There were no significant

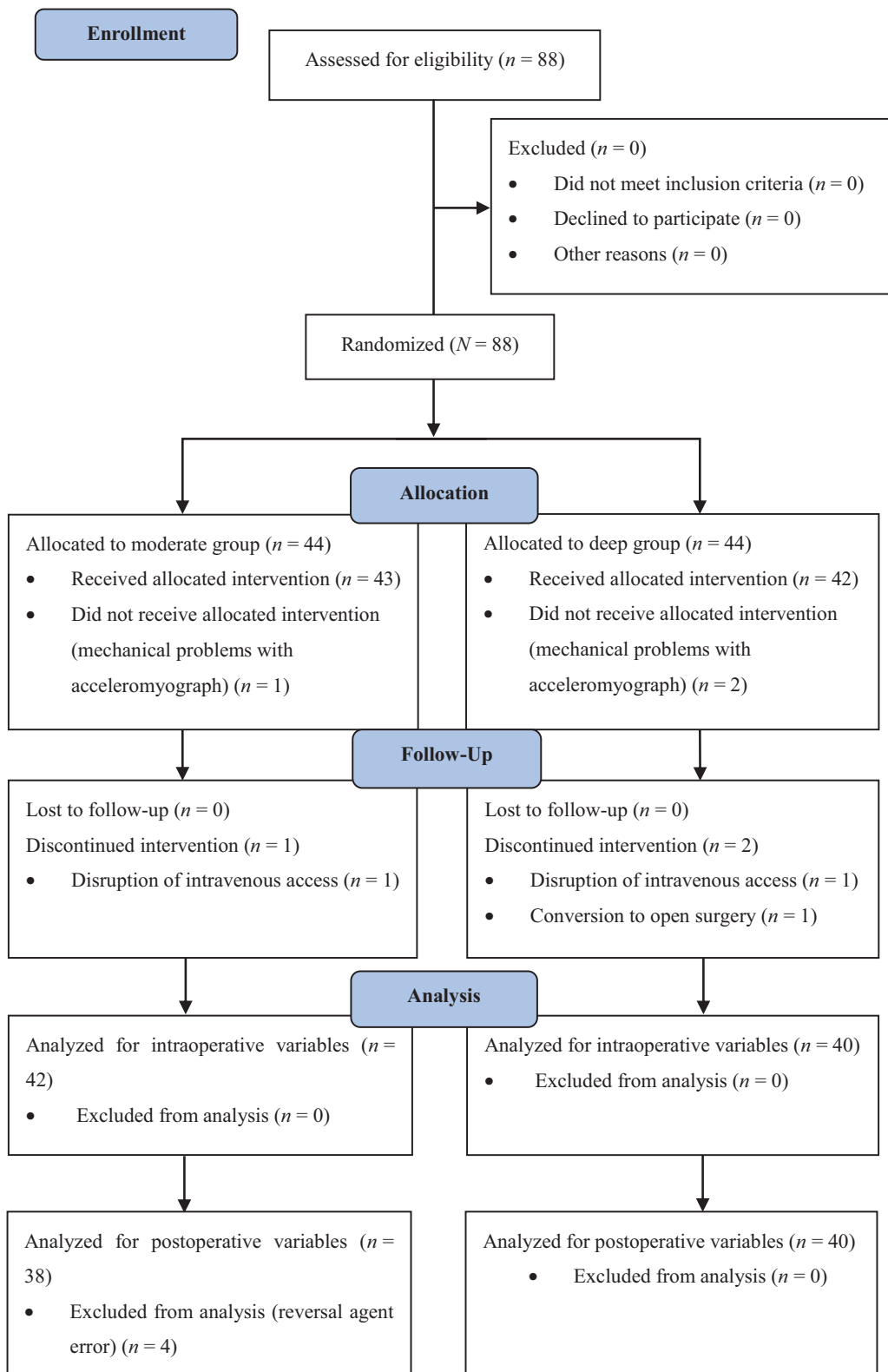


Figure 1. CONSORT diagram.

differences in patient or surgical characteristics between the groups (Table 1).

Table 2 shows the doses of anesthetic drugs used during surgery. Doses of propofol and remifentanyl showed no

significant differences between groups, while the dose of rocuronium was significantly higher in the deep group.

The incidence of intraoperative patient movement was significantly lower in the deep group. There was no significant

Table 1
Patient and surgical characteristics.

	Moderate group (n = 42)	Deep group (n = 40)
Age, years	61.3 (9.8)	62.0 (11.2)
Sex, male/female	28/14	27/13
Height, cm	164.8 (8.6)	163.8 (7.5)
Weight, kg	66.1 (10.1)	65.1 (8.5)
BMI, kg·m ⁻²	24.3 (2.6)	24.3 (2.4)
ASA physical status, I/II	14/28	15/25
Hypertension	16	16
Diabetes	9	7
Surgeon, A/B/C	20/19/3	18/16/6
Duration of surgery, min	150.5 (57.5)	162.0 (65.7)
Duration of anaesthesia, min	204.0 (60.6)	213.5 (67.5)

Continuous values are shown as means (SD). Categorical variables are expressed as number of patients. ASA = American Society of Anaesthesiologists.

difference in surgeon requests for additional NMBA between the groups, but the incidence of actual bolus dose administration was significantly lower in the deep group (Table 3).

Table 4 shows the postoperative recovery and complication data of the patients. The duration of PACU stay was not different between the two groups. However, the postoperative hospitalisation period was significantly longer in the deep group. Respiratory complications were assessed based on the patients' postoperative medical records and chest radiographs on postoperative day (POD) 2. Overall, there were 14 cases of respiratory complications (17.9%), consisting of 11 with radiological evidence of atelectasis, 2 with pneumonic consolidation and 1 with pleural effusion. Surgical site complications occurred in eight patients (10.3%), and included wound dehiscence, seroma and wound infection. There were two reoperations, one of which was ileostomy formation due to anastomosis site leakage; another one was wound revision. There were no significant differences in the rates of postoperative complications between the two groups.

4. Discussion

To our knowledge, this is the first study focusing on the effects of deep NMB on the requirement for intravenous anesthetic agents: no differences were found between the deep and moderate groups.

In this study, BIS was used as an index of anesthetic depth. The BIS uses an empirical algorithm based on three electroencephalography (EEG) domains.^[22] Although BIS has been widely used,

Table 2
Doses of anaesthetic drugs used during surgery.

	Moderate group (n = 42)	Deep group (n = 40)	P-value
Total dose			
Propofol, mg	1680.8 (601.2)	1697.8 (567.7)	.896
Remifentanyl, µg	1095.1 (562.0)	1083.3 (485.2)	.367
Rocuronium, mg	95.2 (24.2)	148.4 (42.7)	.003
Dose per weight and time			
Propofol, mg·kg ⁻¹ ·h ⁻¹	7.54 (1.66)	7.42 (1.01)	.361
Remifentanyl, µg·kg ⁻¹ ·h ⁻¹	4.84 (1.74)	4.79 (1.77)	.710
Rocuronium, mg·kg ⁻¹ ·h ⁻¹	0.44 (0.11)	0.67 (0.17)	.006

Values are presented as means (SD).

Table 3
Rates of intraoperative patient movement, surgeon requests for additional NMBA and bolus NMBA administration.

	Moderate group (n = 42)	Deep group (n = 40)	P-value
Patient movement	18 (42.9%)	9 (22.5%)	.050
Number of movements	1.83 (0.99)	1.44 (0.53)	.395
Surgeon requests for additional NMBA	32 (76%)	24 (60%)	.115
Number of requests (Surgeon A/B/C)	3.22 (1.91) 2.2/4.2/1.0	2.75 (1.70) 1.6/3.25/2.0	.354
Bolus NMBA administration	32 (76%)	21 (53%)	.007
Number of bolus NMBA	2.00 (1.24)	2.16 (1.30)	.570

Categorical variables are expressed as numbers of patients (%). Continuous values are shown as means (SD). NMBA = neuromuscular blocking agent.

it has been criticized based on several points, including the time delay, unreliability under certain conditions (e.g., in older patients and those with underlying brain disease, and in the context of N₂O or ketamine use), and failure to detect intraoperative awareness.^[23,24] Additionally, electrical activity of the muscles, as measured by electromyography (EMG), is known to be an important source of EEG interference.^[23] This can be explained by the high frequency nature of EMG signals (30–300 Hz), which overlaps the range of EEG (0–50 Hz) and elevates the BIS value.^[25] Several studies including conscious volunteers or lightly sedated patients reported a decrease in the BIS after administration of NMBAs, and an increase following reversal of NMB, but with no effect on actual EEG activity.^[26–29] In contrast, the effect of NMB on the BIS value is controversial with respect to the states of deep sedation and general anesthesia. Administration of NMBA decreased the BIS value during moderate sedation, but it had no effect during deep sedation in critically ill patients.^[30] However, administration of NMBA decreased the BIS value, while the reversal agent increased the BIS value during steady-state remifentanyl/propofol anesthesia.^[25,31] This has also been observed during steady-state desflurane anesthesia.^[32] While these studies all indicate that EMG activity affects the BIS value, they all evaluated either the effect of a bolus dose of NMBA or reversal agent on the BIS value. Our results are important because they show no difference in BIS-guided administration of propofol to maintain stable anesthesia during surgery between moderate and deep NMB. Some muscle activity occurred in both groups and significantly more activity was evident in the moderate group. However, there was no difference in the dose of propofol administered to maintain a BIS value of 40–50.

Table 4
Postoperative recovery and complication data.

	Moderate group (n = 38)	Deep group (n = 40)	P-value
Duration of PACU stay, min	33.1 (13.6)	35.9 (16.1)	.346
Postoperative hospital stay, days	6.4 (1.2)	7.8 (3.1)	.023
Respiratory complications	6 (15.8%)	8 (20%)	.628
Surgical site complications	5 (13.2%)	3 (7.5%)	.476
Reoperation	1 (2.6%)	1 (2.5%)	1.000

Continuous values are presented as means (SD). Categorical variables are expressed as numbers of patients (%). PACU = post-anaesthesia care unit.

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Intraoperative patient movement was detected in an unexpectedly high proportion of patients. Although it was significantly more frequent in the moderate group, movement was also detected in 22.5% of the deep group patients. However, the majority of movement was noticed as dimpling in the ET_{CO}₂ curve without gross patient movement; gross patient movement was very rare. The diaphragm is known to be one of the most resistant muscles to NMB and may recover faster than other peripheral muscles. According to a previous study, 20% of patients with a PTC of 1, and more than 30% with a PTC of 2, showed a response when the carina was directly stimulated; moreover, the response rate increased in proportion to the number of PTCs.^[33] Given that the remifentanyl dose was relatively low and not different between our groups despite a difference in the incidence of movement, inadequate control of analgesia cannot be ruled out. If the analgesia dose was also determined by objective indicators rather than vital signs, intraoperative movement may have been prevented more efficiently. Monitoring of the patient stress level has recently been introduced, for example by using the analgesia nociception index (ANI), which is derived from wavelet transform analysis of heart rate variability. A recent study reported that remifentanyl titration based on the ANI minimized reactivity during surgery and reduced the remifentanyl requirement by efficiently controlling nociception, thereby reducing opioid-induced hyperalgesia and the opioid demand after surgery.^[34] Addition of another opioid-sparing agent (e.g., alpha-2 agonist, lidocaine, or MgSO₄) may also have improved the analgesia.

It is interesting that the rate of surgeon requests for additional NMBA was not significantly different between the groups, although the rate of actual administration of rescue NMBA was significantly lower in the deep group. Requests for additional NMB reflect the surgeon's subjective judgment that the surgical field is not sufficiently secured, or that progression of the procedure will be difficult, even without obvious diaphragmatic or abdominal muscle contraction. In contrast, actual bolus NMBA administration was based on objective neuromuscular monitoring. The number of requests for additional NMBA varied considerably among the three surgeons involved in the study, and relevance with the depth of NMB and the incidence of patient movement were relatively low. This raises questions regarding the reliability of requests for rescue NMBA as an indicator of the efficacy of a deep block.

The postoperative hospitalization period was longer in the deep group, but it is unclear whether this result has clinical significance. Two patients remained hospitalized for more than 2 weeks postoperatively, and both were included in the deep group. One was a 25-year-old woman who had undergone total proctocolectomy for familial adenomatous polyposis; she remained hospitalized for 21 days to preserve ova and to undergo further evaluation for adjuvant chemotherapy. The other patient was a 66-year-old man who remained hospitalized for 15 days because of postoperative ileus and acute kidney injury with subsequent volume overload. Excluding these 2 patients, there was no significant difference in the postoperative stay between the groups ($P=.075$).

This study had some limitations. Firstly, the sample size was insufficient to verify group differences in postoperative complications. The presence of residual NMB has a larger impact on postoperative patient outcome than the depth of intraoperative NMB. However, we used sugammadex to reverse NMB and confirmed recovery to a TOF ratio ≥ 0.9 before extubation in

both groups. Hence, the possibility of postoperative residual NMB was minimized such that the postoperative outcomes can be considered mainly related to the intraoperative depth of NMB. The effect of deep NMB itself on postoperative patient outcome is not well documented compared to that of residual NMB. The surgical stress response, as measured by cytokines, is not different between moderate and deep groups.^[35] Deep NMB during laparoscopic surgery improves the surgical space condition and reduces postoperative pain.^[36] A recent bariatric surgery study demonstrated that poor surgical space condition was improved by switching from moderate to deep NMB, and surgical complications increased significantly in patients in a poor surgical space condition.^[37] Further study is needed to confirm the effect of deep NMB on patient outcomes.

Secondly, the target BIS range rather narrow (40–50), compared with the more commonly used range of 40–60, to ensure a stable anesthetic state. Results may differ according to the target BIS range. Thirdly, intraoperative BIS values were not analyzed. Due to the rapidly fluctuating nature of the BIS, a value documented at a certain time may be of limited significance; however, if the continuously recorded values had been collected from the BIS device, they would have supported the results. Fourthly, only relatively healthy (ASA 1–2) patients were included in the study. Considering that the majority of colorectal cancer patients are elderly, and that ASA 3 is fairly common, this inclusion criterion may have led to selection bias.

In conclusion, deep NMB did not reduce the BIS-guided propofol requirement during laparoscopic colon surgery compared to moderate NMB, despite reducing intraoperative patient movement and the requirement for a rescue NMBA.

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