의학 석사 학위논문

The effect of depth of neuromuscular blockade on propofol requirement during laparoscopic colorectal surgery under total intravenous anesthesia

전정맥마취 하 복강경 대장 수술 중
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프로포폴 요구량에 미치는 영향

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Abstract

Introduction. Deep neuromuscular blockade is considered beneficial in improving the surgical condition in laparoscopic surgeries. In moderate block, poor surgical condition might lead to a need for an increase in the depth of anesthesia, which is related to adverse postoperative outcomes. In this study, we investigated whether deep block can reduce the requirement of propofol used in laparoscopic colorectal surgery.

Methods. Adult patients undergoing elective colorectal surgery were randomly allocated to moderate or deep neuromuscular block group. TOF count 1-2 in moderate group, and PTC 1-2 in deep group was maintained through continuous infusion of rocuronium. The induction and maintenance of anesthesia was done by TCI of propofol and remifentanil, and the dose of propofol and remifentanil used were recorded at the end of surgery. The incidence of intraoperative patient movement, additional NMB administration and postoperative complications were also documented.

Results. A total of 82 patients were included in the analyses. Average dose of propofol used was 7.54 ± 1.66 vs 7.42 ± 1.01 ($mg.kg^{-1}.hr^{-1}$, mean $\pm$ S.D, moderate group vs deep group, P=0.104). Average dose of remifentanil used was 4.84 ± 1.74 vs 4.79 ± 1.77 ($\mu g.kg^{-1}.hr^{-1}$, P=0.688). Incidence of

intraoperative patient movement (42.9% vs. 22.5%, p=0.050) and additional NMB administration (76% vs. 53%, p=0.007) were significantly reduced in deep group. Postoperative complications including pulmonary complication, wound problem, re-operation showed no difference between the groups.

Conclusion. Despite the effect of reducing intraoperative patient movements and rescue NMB administration, deep block could not reduce the requirement of propofol during laparoscopic colorectal surgery. It indicates that depth of anesthesia and neuromuscular blockade is considered separately, and the dose of intravenous anesthetic agents cannot be reduced based upon deep block.

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Keywords: neuromuscular blockade, laparoscopy, colorectal surgery, general anesthesia, propofol, postoperative complications

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Introduction

Since sugammadex was introduced, researches on potential benefits of deep neuromuscular blockade have been conducted in various aspects. Among the advantages, improvement of surgical condition in laparoscopic surgeries is supported by the most evidence. Researches indicated that deep block, compared to moderate block, facilitates higher surgical condition ratings score, enables lower pressure pneumoperitoneum, prevents advertent patient movement and reduces pain scores at immediate postoperative period. [1-7]

On the other hand, whether deep block affects the dose of anesthetic agents has not been studied so far. Previous studies revealed that moderate block was insufficient to attain an acceptable surgical condition in a considerably high rate. Therefore, we hypothesized that there could be a tendency to improve the inadequate surgical condition by increasing the depth of anesthesia.[7, 8]

Deep anesthesia, mostly represented by low values of bispectral index, is associated with increased adverse outcomes, including postoperative mortality.[9-12] Some researchers argued that this is an epiphenomenon following other factors like age, co-morbidities or hemodynamic instability. [13, 14] However, considering the reports on neurotoxicity, cardiovascular depression, proinflammatory and immunosuppressive effects of general

anesthetic agents, it cannot be ruled out that adverse outcomes are dose-dependent, and that minimizing the dose of anesthetic agents can improve the outcomes. [9, 15-20]

The aim of this study was to investigate whether deep block reduces the requirement of propofol during total intravenous anesthesia in laparoscopic colorectal surgery, compared to moderate block.

Materials and methods

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

Patients aged 19-75 years scheduled for elective colorectal surgery for colorectal cancer at Seoul National University Bundang Hospital (SNUBH) were included. Exclusion criteria was ASA physical status ≥ 3, body mass index (BMI) < 18.5 or ≥ 35 kg.m^{-2}, history of severe cardiopulmonary, renal or hepatic disease, pregnancy, history of hypersensitivity to anesthetic agents or neuromuscular blocking 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 moderate or deep neuromuscular block group using a set of computer-generated random numbers kept in sealed envelopes.

At the entrance of the operating theater, the patients were premedicated with 0.03 mg.kg^{-1} of midazolam. After monitoring of non-invasive blood pressure, 3-electrode electrocardiogram, pulse oximetry, bispectral index (BIS ™ Quattro, Medtronic, Minneapolis, MN, USA) was started, acceleromyography (TOF-Watch®SX, Organon Ireland Ltd., a subsidiary of Merk and Co., Swords, Co. Dublin, Ireland) was applied to the patient. Two pediatric surface electrodes were placed over the right ulnar nerve with a distance of 3–6 cm, the transducer was attached to the thumb and the other 4 fingers were immobilized.

For induction of anesthesia, target controlled infusion (TCI) of propofol 4.0 ng.ml^{-1} and remifentanil 3.0 ng.ml^{-1} was used. After the patient's loss of consciousness, a 50 Hz tetanus stimulus was applied for 5 seconds. Followed by stabilization and calibration of acceleromyography, rocuronium 0.6 mg.kg^{-1} was administered, and the tracheal intubation was done after the loss of all the Train-of-Four (TOF) responses.

Anesthesia was maintained with TCI of propofol and remifentanil to keep BIS 40-50 and systolic blood pressure within 20% of ward measurements. In moderate group, TOF count 1-2, and in deep group, Post-tetanic count (PTC) 1-2 was maintained through continuous infusion of rocuronium. TOF and PTC were monitored every 15 seconds and 5 minutes respectively, and the dose of rocuronium was adjusted in 0.1 mg.kg^{-1}. hr^{-1} increments according to the TOF

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count and the PTC. If the surgeon requests additional neuromuscular blockade, additional 5 mg of rocuronium was given if TOF $\geq$ 2 in moderate group or PTC $\geq$ 2 in deep group. On the other hand, if TOF < 2 in moderate group or PTC < 2 in deep group, dose of remifentanil was increased without additional neuromuscular blockade.

At the end of surgery, the patients were given either neostigmine with glycopyrrolate or sugammadex (Bridion®, Merck Sharp and Dohme (MSD), Oss, Netherlands), and were extubated when the TOF ratio became more than 0.9.

Movements of the patient including gross movements and self-respiration on end-tidal carbon dioxide ($ETCO_2$) graph, surgeon's request for additional NMB and actual bolus NMB administration was documented during the surgery. Doses of propofol and remifentanil used, operating time, anesthesia time, PACU stay time were also recorded. Additionally, length of postoperative hospital stay and postoperative complications including respiratory complications, surgical site complications, re-operation within 30 days were reviewed after the patients were discharged.

Statistical analysis

Dose of propofol used during anesthesia was the primary outcome variable. The secondary outcome variables were the dose of remifentanil used, intraoperative patient movement, surgeon's request for additional NMB, bolus NMB administration and postoperative complications.

Based on a previous study, the dose of propofol used during laparoscopic cholecystectomy with moderate block was 7.25 $mg.kg^{-1}.hr^{-1}$ (SD = 1.13).[1] The sample size of 44 patients in each group was estimated to detect a 20% difference between the groups, with 5% type 1 error risk, 80% power and 10% dropout rate.

The groups were compared with student's t-test or Mann-Whitney U test for continuous variables and chi-square test or fisher's exact test for non-continuous variables, using SPSS 25.0 software for Windows (SPSS Inc., Chicago, IL, USA). A P-value <0.05 was considered statistically significant.

Results

A total of 82 patients were included in the analyses. There were 88 eligible patients enrolled in the study. Three of the cases had to quit neuromuscular monitoring due to the mechanical problems, two needed temporary supplement of inhaled anesthetics to maintain anesthesia because of malfunction of the intravenous access, and one was conversed to an open surgery. Three surgeons were involved in the study, and they were represented as surgeon A, B, C. Estimated blood loss was minimal in the majority of the patients and there was no case requiring transfusion. The patient and surgery characteristics are presented in Table 1, and there was no significant difference between the groups.

Table 2 shows the doses of anesthetic drugs used during surgery. Dose of propofol and remifentanil showed no statistical difference, and dose of rocuronium was significantly higher in deep group.

The incidence of intraoperative patient movement was significantly reduced in deep group. Surgeon's request for additional neuromuscular blockade showed no statistical difference between the groups, but the incidence of actual bolus dose administration was significantly reduced in deep group. (Table 3)

Table 4 shows postoperative recovery and complications of the patients. Duration of PACU stay and postoperative hospitalization days were not

different between the two groups. Respiratory complications were assessed based on the patients'postoperative medical records and chest radiograph at post-operative day (POD) 2. There were overall 14 respiratory complications (17.0%). 11 of them showed radiologic evidence of atelectasis, 2 developed pneumonic consolidation and 1 had pleural effusion. Surgical site complications occurred in 9 patients (11.0%), that included wound dehiscence, seroma and wound infection. There were three re-operations, one of which was ileostomy formation due to anastomosis site leakage, and two of them were wound revisions. All of the postoperative complications showed no statistical difference between the two groups.

Figure 1. CONSORT flow diagram.
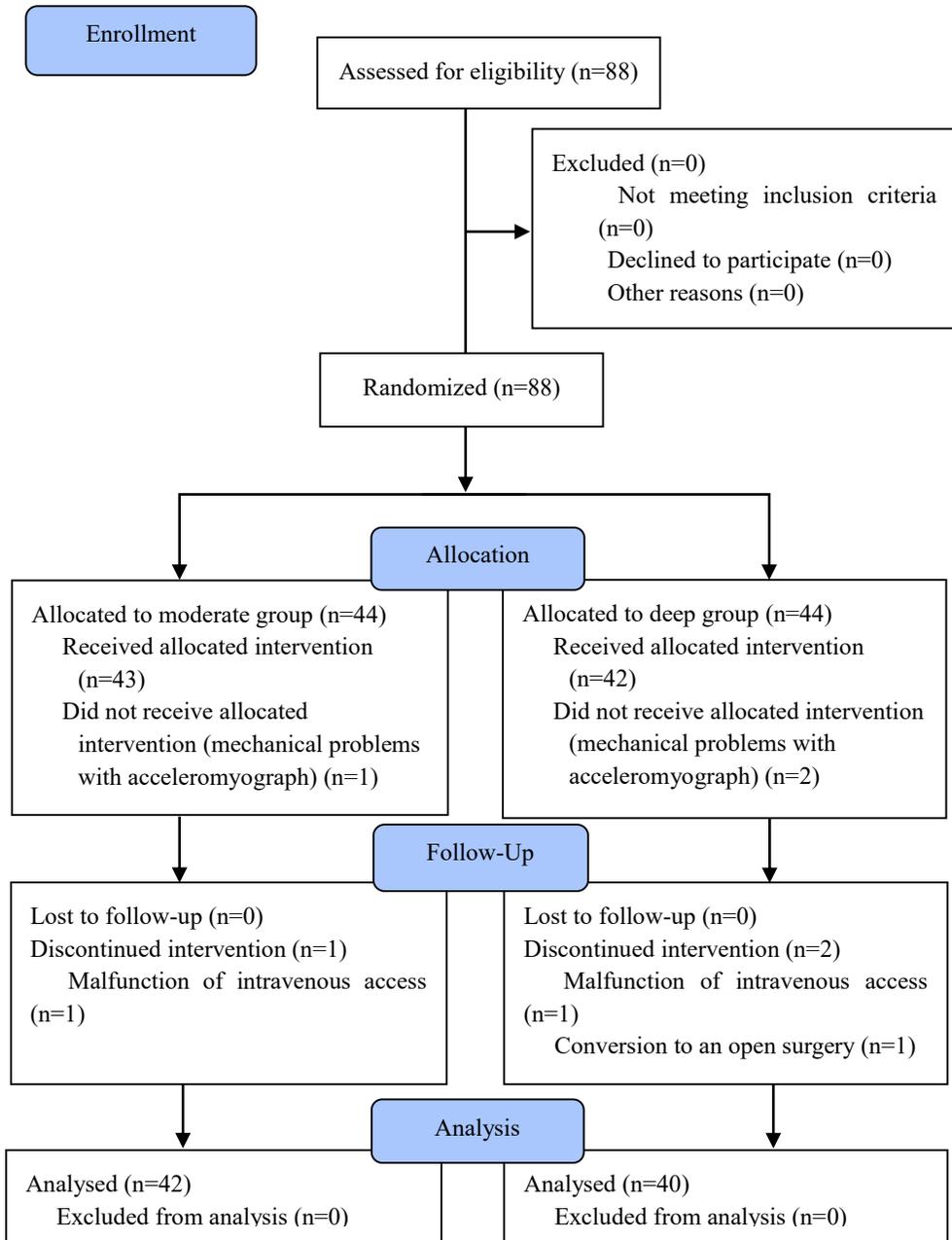
Table 1. Patient and surgery characteristics.

	Moderate group ($n = 42$)	Deep group ($n = 40$)	p-value
Age (year)	61.3 (9.8)	62.0 (11.2)	0.729
Gender (male/female)	28/14	27/13	0.936
Height (cm)	164.8 (8.6)	163.8 (7.5)	0.262
Weight (kg)	66.1 (10.1)	65.1(8.5)	0.390
BMI ($kg.m^{-2}$)	24.3 (2.6)	24.3 (2.4)	0.596
ASA physical status (I/II)	14/28	15/25	0.693
Hypertension	16	16	0.860
Diabetes	9	7	0.654
Surgeon (A/B/C)	20/19/3	18/16/6	0.518
Duration of surgery (min)	150.5 (57.5)	162.0 (65.7)	0.301
Duration of anesthesia (min)	204.0 (60.6)	213.5 (67.5)	0.495

Continuous values are shown as mean (SD). Categorical variables are expressed as number of patients. ASA, american society of anesthesiologists.

Table 2. Doses of anesthetic 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)	0.896
Remifentanil (µg)	1095.1 (86.7)	1083.3 (485.2)	0.367
Rocuronium (mg)	95.2 (3.7)	148.4 (42.7)	0.003
Dose per weight and time			
Propofol (mg.kg^{-1}.hr^{-1})	7.54 (1.66)	7.42 (1.01)	0.361
Remifentanil (µg.kg^{-1}.hr^{-1})	4.84 (1.74)	4.79 (1.77)	0.710
Rocuronium (mg.kg^{-1}.hr^{-1})	0.44 (0.11)	0.67 (0.17)	0.006

Values are presented as mean (SD).

Table 3. Incidence of intraoperative patient movement, surgeon's request for additional NMB and bolus NMB administration.

	Moderate group ($n = 42$)	Deep group ($n = 40$)	p-value
Patient movement	18 (42.9%)	9 (22.5%)	0.050
Surgeon's request for additional NMB	32 (76%)	24 (60%)	0.115
Bolus NMB administration	32 (76%)	21 (53%)	0.007

Categorical variables are expressed as number of patients (%).

Table 4. Postoperative recovery and incidence of complications.

	Moderate group (*n* = 42)	Deep group (*n* = 40)	*p*-value
Duration of PACU stay (min)	32.9 (13.3)	35.9 (16.1)	0.522
Postoperative hospital stay (day)	6.7 (2.1)	7.8 (3.1)	0.092
Respiratory complications	6 (14.3%)	8 (20%)	0.492
Surgical site complications	6 (14.3%)	3 (7.5%)	0.483
Re-operation	2 (4.8%)	1 (2.5%)	1.000

Values are presented as mean (SD). Categorical variables were expressed as patient number. PACU, post-anesthesia care unit.

Discussion

To our best knowledge, this is the first study focused on the effect of deep neuromuscular blockade on the requirement of intravenous anesthetic agent, yet no difference was found between deep and moderate group. Although a few researchers suggested the "afferent muscle spindle theory", which implies the possibility that neuromuscular blockade can indirectly affect the cerebral arousal state by reducing the afferent signal from muscle activity, it is currently a standard knowledge that neuromuscular blocking agents have no direct effect on the depth of sedation. [22-25] Therefore, this research is based on the assumption that intravenous anesthetic agents and rocuronium have no pharmacological interaction.

The result shows that there was no tendency to compensate for the lack of neuromuscular blockade with increased depth of anesthesia. Advances in monitoring equipment, such as bispectral index (BIS), have made it easier to discriminate whether anesthesia depth is sufficient when an inadvertent patient movement occurs during surgery. Besides, conventional concerns about delayed neuromuscular recovery or residual curarization have been largely overcame by the development of sugammadex and quantitative neuromuscular monitoring devices. Such a precise distinction between anesthetic depth and neuromuscular block depth could be rather seen as a desirable trend, which

enables adequate patient management while avoiding adverse outcomes following deep anesthesia. From a clinical perspective, this result also supports the fact that the dose of intravenous anesthetic agents should not be reduced based on the depth of neuromuscular blockade.

In this study, BIS was used as an index of anesthesia depth. This may be a confounding factor in a research dealing with neuromuscular blockade. BIS is an indicator based on empirical algorithm that combines three domains derived from electroencephalography (EEG), and electromyographic (EMG) signal from facial muscles is processed and displayed as a separate parameter.[26] However, the interference in BIS value by EMG signals has been a consistent issue of controversy. Several studies, mainly in awake volunteers or during a sedation in intensive care unit(ICU) patients, reported a decrease in BIS after administration of neuromuscular blocking agents, and an increase after neuromuscular reversal, without affecting the actual EEG activity.[27-29] These results raised the concern for the risk of inadequately light sedation and awareness in ICU, particularly during neuromuscular blockade. On the other hand, in a state of deep sedation or general anesthesia, neuromuscular blockade did not seem to affect BIS value.[22, 25] It is most reasonably explained by the high frequency nature of EMG, 30-300Hz of which overlaps 0–50 Hz of EEG, particularly in the fast portion of EEG waves, and cause an elevation in BIS value.[25] The result of current study supports the previous findings that in the

state of general anesthesia and moderate to deep neuromuscular block, the majority of EMG activity is blocked and the influence on the BIS would be minimal.

The incidence of intraoperative patient movement was reduced in approximately half in deep group, and administration of additional NMB bolus was also significantly reduced. Our result well correlates with previous studies, and although surgical condition score was not investigated in current study, this seems to be a factor that contributes to surgeon's satisfaction with the surgical conditions. [1, 30] Nonetheless, intraoperative patient movement and rescue NMB administration were reduced but could not be completely prevented in deep block group either. It indicates that during an operation, the intensity of surgical stimuli varies according to its process, and at some point intense neuromuscular blockade might be temporarily required to gain more surgical space or block the reflex movements.[31] Whether a routine administration of intense block is necessary should be decided with discretion considering the benefits and the costs.

It is interesting that the incidence of surgeon's requests for additional NMB did not show significant difference between the groups, despite that actual administration of rescue NMB was significantly less in deep group. The requests for additional NMB reflects surgeon's subjective judgment that the

surgical field is not sufficiently secured or the progression of the procedure is difficult, even without obvious diaphragm or abdominal muscle contraction. In contrast, actual bolus NMB administration was based on objective neuromuscular monitoring. The number of requests from 3 surgeons who were involved in the study showed considerable variation, and even one of them was increased in deep group. This difference may be partially due to individual preferences and operating styles of each surgeon, but the subjectivity raises the question in the reliability of the requests for rescue NMB as an indicator for the efficacy of deep block.

Another explanation is that the requests were related to other factors affecting the field of vision in addition to neuromuscular blockade. The quality of the working space can determined by multiple other factors, including non-modifiable factors such as patients' obesity or history of abdominal surgery, and modifiable factors such as intra-abdominal pressure, position or type of anesthesia. [32] Though their effect was intended to be reduced through the exclusion criteria of BMI and previous surgical history, the frequency of requests for additional NMB still seemed to be partly related to other patient characteristics that make the surgical procedures more challenging, including central obesity, muscularity, and the size of the pelvic cavity. Further researches on the factors that affect surgical conditions could be beneficial.

Despite the improvement in the surgical condition, there is scarce evidence supporting its clinical relevance that deep block affects major patient outcomes. However, a recent study in gastric bypass surgery demonstrated that surgical complications were significantly increased in the patients with poor surgical conditions, and switching from moderate to deep block in those patients could prevent them. [33] Other than that, there were a few retrospective reports that indicated deep block is associated with reduced postoperative complication and unplanned 30-day readmission. [34, 35]

In this study, patient outcomes including postoperative hospital stay, pulmonary complications and surgical site complications were investigated, in which we could not find significant differences. Overall considerably high incidence (17%) of pulmonary complication was observed and majority of them consisted of atelectasis. It seems to be a result of a relatively long time of pneumoperitoneum and extreme trendelenburg position for colorectal surgery. Considering the dose of propofol and remifentanil was equivalent and only the dose of rocuronium increased by 1.5 times in deep group, no difference in lung complication and the PACU stay time between the groups indicates that thorough quantitative neuromuscular monitoring and sugammadex minimized the risk of residual curarization and delayed recovery after deep block. On the other hand, considering the low incidence of surgical site complications and re-operations, we believe that a larger study is required to confirm the relationship

of deep neuromuscular blockade and surgical complications.

This study has some limitations. First, the sample size is small that it was not enough to verify the statistical significance of the postoperative complications. In addition, an organized scoring system for postoperative complication, such as Clavien-Dindo classification, was not used, which could have made the analysis more feasible and effective. Third, this study was performed in a relatively short time scale, and evaluation for the long-term patient outcome was not available. Further research on the long-term outcome variables, for instance 1-year mortality, is needed to validate the true benefits of deep neuromuscular blockade.

Conclusion

Despite the effect of reducing intraoperative patient movements and rescue NMB administration, deep block could not reduce the requirement of propofol during laparoscopic colorectal surgery. It indicates that depth of anesthesia and neuromuscular blockade is considered separately, and the dose of intravenous anesthetic agents cannot be reduced based upon deep block.

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국 문 초 록

연구 배경. 깊은 신경근 차단은 복강경 수술의 여건을 향상시키는 것으로 알려져 있다. 중등도 신경근 차단에서는 부적절한 수술 여건을 보완하고자 마취 깊이를 증가시키는 경향이 있을 수 있으며, 이는 수술 후 불량한 환자 예후와 관련이 있다. 본 연구에서는 깊은 신경근 차단이 중등도 신경근 차단에 비해 전신 마취 하 복강경 대장·직장 수술 중 프로포폴의 요구량을 감소시키는지 알아보고자 하였다.

연구 방법. 정규 대장·직장 수술을 받는 성인 환자를 대상으로 중등도 또는 깊은 신경근 차단 군으로 무작위 배정한 다음, 로큐로니움의 지속 정주를 통해 중등도 신경근 차단 군에서는 사연속자극 1-2, 깊은 신경근 차단 군에서는 강직후연축반응수 1-2를 유지하였다. 프로포폴과 레미펜타닐의 목표농도주입법을 이용하여 마취 유도 및 유지를 시행하였고, 수술 종료 시 사용된 프로포폴과 레미펜타닐의 용량을 기록하였다. 수술 중 환자의 움직임, 집도의의 추가 신경근 차단제 투여 요청 및 실제 추가 투여 여부를 기록하였으며, 수술 후 의무기록을 통해 합병증 발생 여부를 확인하였다.

연구 결과. 총 82명의 환자가 결과 분석에 포함되었다. 수술 중 사용된 프로포폴의 용량은 7.54 ± 1.66 대 7.42 ± 1.01 (mg.kg^{-1}.hr^{-1}, 평균 ± 표준편차, 중등도 대 깊은 신경근 차단 군, p=0.104) 였으며, 레미펜타닐의 용량은 4.84 ± 1.74 대 4.79 ± 1.77 (μg.kg^{-1}.hr^{-1}, p=0.688) 였다. 수술 중 환자의 움직임 (42.9% 대 22.5%, p=0.050) 과 추가 신경근 차단제 투여 (76% 대 53%, p=0.007)의 발생률은 깊은 신경근 차단 군에서 유의하게 감소하였다. 수술 후 폐 합병증, 수술 창상 합병증, 재수술의 발생률은 군간 차이를 보이지 않았다.

결론. 깊은 신경근 차단은 중등도 신경근 차단에 비해 전신 마취 하 복강경 대장·직장 수술 중 환자의 움직임과 추가 신경근 차단제 투여를 줄이지만, 프로포폴의 요구량을 감소시키지는 못한다. 본 연구 결과는 마취 깊이와 신경근 차단의 깊이가 임상적으로 명확히 구분되며, 깊은 신경근 차단에 근거하여 정맥 마취제의 용량을 줄일 수 없음을 시사한다.

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주요어: 신경근 차단, 복강경, 대장·직장 수술, 전신 마취, 프로포폴, 수술 후 합병증

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