

Effects of ultrasound-guided transversus abdominis plane block and rectus sheath block on stress hormone response after laparoscopic colorectal surgery

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Abstract

We examined the effects of ultrasound-guided abdominal peripheral nerve blocks (PNBs) when combined with opioid analgesia on postoperative stress hormones as well as the postoperative clinical course in patients undergoing laparoscopic colorectal surgery. A total of 85 patients were enrolled in this study. The patients were randomly allocated to an opioid only group (group H) or abdominal PNBs (ultrasound-guided transversus abdominis plane block and rectus sheath block) combination group (group L + PNBs) according to the method of postoperative analgesia. The plasma catecholamine (epinephrine, norepinephrine, and dopamine) levels and serum cortisol levels were measured three times:

soon after induction of anesthesia (T1), just before extubation (T2), and in the morning on postoperative day 1 (T3). Visual analog scale (VAS) score, and the occurrence of postoperative nausea and vomiting (PONV) were then recorded. Epinephrine levels were significantly lower in group L+PNBs than in group H at T3. Group L + PNBs experienced lower VAS scores at T3 and less PONV until postoperative day 3 than group H. Combining abdominal PNBs with opioid analgesics for postoperative analgesia in patients undergoing laparoscopic colorectal surgery is effective in terms of postoperative stress control, pain relief and suppressing the occurrence of PONV.

Key words : laparoscopic surgery, stress hormone, transversus abdominis plane block, rectus sheath block, postoperative analgesia

I. Introduction

In recent years, less invasive laparoscopic surgery has been used increasingly to treat colorectal cancer. While this approach has

dramatically reduced postoperative pain, the choice of postoperative analgesia for patients who have undergone laparoscopic colorectal surgery remains controversial. Peripheral nerve blocks (PNBs) are locoregional anesthesia techniques of growing interest in laparoscopic surgery. They are reported to have an analgesic

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effect that is comparable to that of epidural analgesia in the early postoperative period¹⁾. The guidelines now mention that opioid analgesics and PNBs can be used as an alternative for achieving analgesia in early postoperative recovery programs^{2, 3)}. Although references on the relationship between PNBs and postoperative stress response are scattered and PNBs have shown certain results⁴⁾, no studies have reported the effect of PNBs on the stress response in laparoscopic colorectal surgery. We hypothesized that combining abdominal PNBs with opioid analgesics may improve postoperative stress control and the postoperative clinical course in patients undergoing laparoscopic colorectal surgery.

II. Materials and methods

This prospective study was approved by the Ethics Committee at Iwate Medical University School of Medicine (approval number: H27-141) and was conducted in accordance with the current Declaration of Helsinki. Written informed consent was obtained prior to surgery from all patients who participated in the study. The study is registered in the UMIN Clinical Trials Registry (UMIN000018239).

1. Patient allocation and exclusion criteria

All patients included in the study were diagnosed with colorectal cancer stage 0 to stage IV using the conventional classification system and were scheduled for laparoscopic surgery. The inclusion criterion was an Eastern Cooperative Oncology Group performance status of 0 to 2. The exclusion criteria were emergency surgery, a contraindication to the medication used for anesthesia, a history of treatment for chronic pain, neurologic disorders, mental illness, inability or refusal to provide

consent, and conversion of laparoscopic to open surgery. The patients were randomly assigned to one of two groups. One group received an opioid only [intravenous patient-controlled analgesia (iv-PCA) with high dose fentanyl] (group H) and the other received an iv-PCA with low dose fentanyl plus abdominal PNBs (group L+PNBs). All patients underwent laparoscopic colorectal surgery between February 2016 and December 2016.

2. Preoperative management and anesthetic procedures

None of the patients were administered pre-anesthetic medication. In the operating room, peripheral intravenous access was obtained, and oxygen inhalation was carried out for 5 minutes, after which general anesthesia was induced using a target-controlled infusion of propofol at a concentration of 2.0-5.0 $\mu\text{g}/\text{mL}$, fentanyl at a dose of 100-200 μg , and remifentanyl at a dose of 0.25-0.5 $\mu\text{g}/\text{kg}/\text{min}$. After confirmation of loss of consciousness, rocuronium was administered at a dose of 0.6-0.9 mg/kg , and tracheal intubation was performed. Mechanical ventilation was set up such that the tidal volume was 6-10 mL/kg , the respiratory rate was 8-15 breaths per minute, and the positive end-expiratory pressure was 3-5 cmH_2O . The end-tidal CO_2 was adjusted to range between 35 and 40 mmHg . A nasogastric tube and a urethral catheter were then inserted, and anesthesia was maintained using a target-controlled infusion of propofol at a concentration of 1.0-3.0 $\mu\text{g}/\text{mL}$ and remifentanyl at a dose of 0.25-1.0 $\mu\text{g}/\text{kg}/\text{min}$. Adjustments of the target effect-site concentration of propofol were made such that the bispectral index values were maintained at 40-60. Additional doses

of rocuronium 10-20 mg were administered as needed. The infusion solution consisted of an acetate or bicarbonate Ringer's solution, which was administered with a colloidal (hydroxyethylstarch 130/0.4/9) solution. At the time of closure of the surgical wound, fentanyl 200 μg and acetaminophen 1,000 mg (or 15 mg/kg for patients weighing less than 50 kg) were administered intravenously as an adjuvant analgesic and droperidol 1.25 mg was administered intravenously as an antiemetic.

In group H, fentanyl was administered as a continuous intravenous infusion at a dose of 0.6 $\mu\text{g}/\text{kg}/\text{h}$ at the time of closure of the surgical wound. When a patient complained of pain, fentanyl could be administered as a bolus of 0.6 $\mu\text{g}/\text{kg}$ once every 30 minutes. Fentanyl and droperidol 5 mg were mixed together in a physiologic saline solution to a total volume of 60 mL. A 60-mL COOPDECH[®] Syrinjector + PCA set (Daiken Medical Co., Ltd, Osaka, Japan) was used as the PCA pump.

In group L+PNBs, fentanyl was administered as a continuous intravenous infusion at a dose of 0.2 $\mu\text{g}/\text{kg}/\text{h}$ at the time of closure of the surgical wound. When there was pain, fentanyl could be administered as a bolus of 0.2 $\mu\text{g}/\text{kg}$ once every 30 minutes. Fentanyl and droperidol 5 mg were mixed together in a physiologic saline solution to a total volume of 60 mL. The same type of PCA pump was used in group L + PNBs as in group H. After completion of surgery, an ultrasound-guided transversus abdominis plane (TAP) block and a rectus sheath block were performed before the patient awoke from anesthesia. A total of 60 mL of levobupivacaine 0.25% was used for the PNBs (15 mL of levobupivacaine 0.25% was injected per each PNB).

After completion of the operation, administration of propofol and remifentanyl was terminated, and sugammadex 2-4 mg/kg was administered intravenously. After extubation, the patient was then transferred to the recovery room and kept under observation for 30-60 minutes, and subsequently moved to the hospital ward.

3. Surgical procedure

The surgery was performed with the patient in the lithotomy position. Five ports were used, comprising one blunt port (blunt tip trocar) above the umbilicus, one 12-mm port, and three 5-mm ports. The blunt port in the umbilical region was extended for the small incisional wound, and the length of the surgical wound was set to less than 5 cm.

4. Postoperative management

Intake of clear fluids and water was permitted on the morning of postoperative day 1 at the discretion of the attending surgeon. Oral feeding was resumed after confirmation of passage of flatus or bowel movements. When there was pain, PCA was administered as a bolus infusion, and when analgesia was insufficient, flurbiprofen 50 mg and/or buprenorphine 0.2 mg was administered as an intravenous infusion. The iv-PCA was discontinued in the event of drowsiness or occurrence of postoperative nausea and vomiting (PONV) in accordance with the judgement of doctors.

5. Measurement of study parameters

The plasma catecholamine (epinephrine, nor-epinephrine, and dopamine) levels, and serum cortisol levels were measured three times, i.e., soon after induction of anesthesia (T1), before extubation (just after PNBs) (T2), and in the morning on postoperative day 1 (T3). At each of these time points, venous blood was collected, left to stand for 120 minutes, and

then centrifuged at 5000 rpm for 10 minutes, after which plasma and serum samples were collected. The severity of pain at T3 was evaluated using the visual analog scale (VAS). The following were then recorded: the number of times additional analgesics were administered, the occurrence of PONV until T3 and postoperative day 3 (T4), the number of days until resumption of oral feeding, and the postoperative length of hospital stay. The anesthesia time, operating time, amount of intraoperative bleeding, doses of crystalloid and colloidal solutions administered, and urine output were recorded upon completion of surgery.

6. Statistical analysis

The preliminary study was conducted prior to this research. In the preliminary study, epinephrine level in the morning on postoperative day 1 was 0.06 ± 0.0352 ng/ml in group H and 0.038 ± 0.0245 ng/ml in group L + PNBs. On the basis of this result, it was found that a significant difference was observed in epinephrine levels in the morning on postoperative day 1, so those levels were established as the primary endpoint. From this result, power analysis was carried out and the effect size was calculated to be 0.7254. Calculations were carried out such that when the α -error was 0.05 and the power was 0.8, the number of samples was 33 per group. The success rate of the abdominal PNBs was estimated at 90%, the number of dropouts was estimated at 10%, and the final number of samples was 41 per group.

All measured values are shown as the mean \pm standard deviation or as the median with the interquartile range in accordance with the data distribution shown by the Shapiro-

Wilk normality test. The unpaired t-test, Mann-Whitney U test, and chi-square test were performed, and a p-value less than 0.05 was considered to be statistically significant. The statistical analyses were carried out using G*Power 3 (Institute for Experimental Psychology, Heinrich-Heine-University, Germany) and GraphPad Prism[®] 7 for Mac (GraphPad Software Inc., San Diego, CA, USA)⁵⁾.

III. Results

Eighty-five eligible patients were enrolled in the study, and 3 were subsequently excluded. One more patient in group L + PNBs was excluded because of conversion to open surgery, leaving 41 patients in group H and 40 patients in group L + PNBs (Fig. 1). The patient characteristics and intraoperative data were comparable between two groups (Table 1). The data from blood samples are shown in Table 2. At T3, epinephrine levels were significantly lower in group L + PNBs than in group H ($p = 0.038$). Norepinephrine, dopamine, and cortisol levels were not significantly different at any time point. The postoperative clinical findings are shown in Table 3. There was no significant difference in the number of times additional analgesics were used, but VAS scores were significantly lower in group L + PNBs than in group H ($p = 0.012$). There was no significant difference in occurrence of PONV until T3, but group L+PNBs experienced significantly less PONV than group H until T4 ($p = 0.013$). No significant difference in the number of days until resumption of oral feeding or postoperative length of hospital stay was found between two groups.

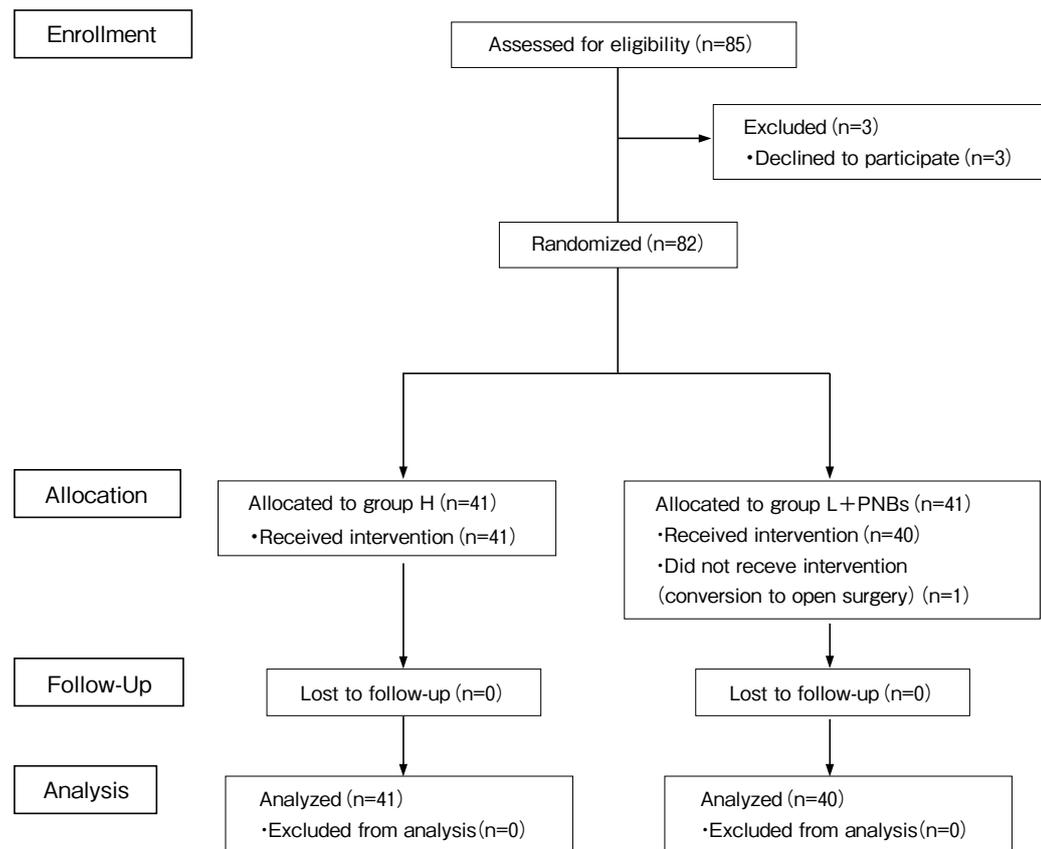


Fig. 1. Consolidated standards of reporting trials (CONSORT) diagram showing the flow of participants

Table 1. Patient characteristics and intraoperative data

	Group H (n=41)	Group L+PNBs (n=40)	p-value
Age (yr)	65.5 ± 11.8	68.4 ± 13.2	0.499
Sex (Male/Female)	27/14	20/20	0.180
Height (cm)	161.5 ± 10.6	158.8 ± 9.5	0.517
Weight (kg)	59.2 ± 11.1	56.7 ± 11.4	0.888
ASA-PS (1/2/3)	6/30/5	7/29/4	0.908
Anesthesia time (min)	261 (240-310)	272 (226-329)	0.783
Operating time (min)	192 (173-241)	199 (163.5-249)	0.849
Blood loss (mL)	19 (8-48)	15 (6-24)	0.237
Crystalloid infusion (mL)	1,200 (980-1,400)	1,000 (862-1,375)	0.064
Colloid infusion (mL)	715 ± 331	500 (400-700)	0.350
Urine output (mL)	520 (187-752)	540 (177-707)	0.975

Values are presented as mean ± standard deviation, numbers, or median (interquartile range). American Society of Anesthesiologist Physical Status, ASA-PS

Table 2. Data from blood samples

	Group H (n=41)	Group L+PNBs (n=40)	p-value
Epinephrine at T1 (ng/mL)	0.02 (0-0.02)	0 (0-0.02)	0.546
Epinephrine at T2 (ng/mL)	0 (0-0)	0 (0-0)	0.746
Epinephrine at T3 (ng/mL)	0.07 (0.04-0.09)	0.04 (0.02-0.08)	0.038
Norepinephrine at T1 (pg/mL)	158 ± 64	120 (72-170)	0.055
Norepinephrine at T2 (pg/mL)	103 ± 47	75 (42-137)	0.256
Norepinephrine at T3 (pg/mL)	250 (190-365)	195 (140-352)	0.160
Dopamine at T1 (ng/mL)	0 (0-0)	0 (0-0)	0.355
Dopamine at T2 (ng/mL)	0 (0-0)	0 (0-0)	0.205
Dopamine at T3 (ng/mL)	0 (0-0)	0 (0-0)	0.668
Cortisol at T1 (μg/dL)	12.2 ± 4.2	11.6 ± 4.9	0.517
Cortisol at T2 (μg/dL)	2.4 (1.8-3.1)	2.6 (1.8-3.6)	0.520
Cortisol at T3 (μg/dL)	15.6 (11.8-19.3)	17.1 ± 6.2	0.549

Values are presented as mean ± standard deviation, numbers, or median (interquartile range).

Table 3. Postoperative clinical findings

	Group H (n=41)	Group L+PNBs (n=40)	p-value
VAS at T3 (mm)	38.8 ± 12.4	31.2 ± 14.1	0.012
PONV until T3 (+/-)	5/36	3/37	0.712
PONV until T4 (+/-)	17/24	6/34	0.013
Discontinuance of iv-PCA	2	0	0.493
Rescue analgesics until T3	1 (0-2)	1 (0-2)	0.434
Rescue analgesics until T4	3 (1-4)	3 (1.2-5)	0.300
Total amount of iv-PCA fentanyl (μg)	2,000 (1,800-2,150)	700 (600-800)	<.00001
Diet resumption (days)	3 (3-3)	2 (2-3)	0.076
Postoperative stay (days)	10 (8-14.5)	7 (6-9)	0.370

Values are presented as mean ± standard deviation, numbers, or median (interquartile range). visual analog scale, VAS; postoperative nausea and vomiting, PONV; intravenous patient-controlled analgesia, iv-PCA

IV. Discussion

In open colorectal surgery, epidural analgesia is believed to be better than intravenous analgesia in terms of pain relief, recovery of intestinal function, and shortening of hospital stay^{6,7)}. In recent years, the prevalence of

laparoscopic colorectal surgery has increased rapidly. There are various arguments regarding postoperative analgesia in laparoscopic colorectal surgery; previous reports have stated that epidural anesthesia should not be used in patients undergoing laparoscopic colorectal

surgery due to the possible complications^{8, 9}. In addition, the number of patients deemed unsuitable for epidural anesthesia has increased due to concerns regarding oral medication, patient comorbidities, and anticoagulant therapy for the prevention of deep vein thrombosis during the perioperative period. Against such a background, PNBs or opioid-based iv-PCA can be considered as alternatives for postoperative analgesia¹⁰. However, opioids also have disadvantages, including decreased gastrointestinal motility, occurrence of PONV, sedation, and respiratory depression. Therefore, PNBs, which exert their analgesic effects via a different mechanism, may be a useful alternative for postoperative pain relief in laparoscopic surgery. Abdominal PNBs have been used often as a component of multimodal analgesia in abdominal surgery, but their efficacy following laparoscopic colorectal surgery is still debated. One study found the TAP block improves postoperative opioid consumption and pain outcomes, but another indicated that it confers no specific advantage in opioid use and pain relief^{11, 12}. No studies have examined the relationship between abdominal PNBs and stress hormones after laparoscopic colorectal surgery. This randomized clinical trial aimed to assess the effects of abdominal PNBs on postoperative stress hormones and the postoperative clinical course in patients undergoing laparoscopic colorectal surgery.

Humans have two major stress response systems, the hypothalamic-pituitary-adrenal axis and the sympathetic-adrenal-medullary system¹³. Catecholamines are markers for the sympathetic-adrenal-medullary system: their levels increase immediately in the presence of stress, and their rate of elimination from the

bloodstream is as short as 3 minutes, whereas cortisol, which is a pituitary-adrenocortical hormone, is believed to reflect a chronic stress response^{14, 15}. Elevated levels of epinephrine and norepinephrine will adversely affect the postoperative course in such factors as cardiac function, immune function, and wound healing. In the present study, epinephrine levels were significantly lower in group L + PNBs at T3. Although there was no significant difference in norepinephrine levels, they also showed a lower trend in group L + PNBs. Because we regarded epinephrine at T3 as a primary outcome and set the number of samples based on the results of our preliminary study, there was a possibility that norepinephrine would not show a significant difference. Cortisol secretion is subject to physiologic diurnal variation, such that cortisol levels are high early in the morning and decrease to their lowest values late at night¹⁵. The inhibition of cortisol levels found at T2 may reflect the influence of diurnal variations in addition to the influence of general anesthesia. In this study, cortisol levels were not significantly different at any time point. We assessed serum total cortisol levels. There are studies suggesting that measuring serum-free cortisol levels may be important, because they may offer more precise assessments of the hypothalamic-pituitary-adrenal axis' activity¹⁶. Our findings regarding cortisol should be interpreted with caution because we did not assess serum-free cortisol nor indirectly calculate the amount of serum-free cortisol. Dopamine showed zero at almost all time points of assessment probably due to the detection threshold, so we could not compare groups for dopamine. From the above assessment of stress hormones, we

believe that stress response has been shown to be mitigated or at least equal by combining PNBs and reducing the dose of fentanyl. This study is the first to investigate the relationship between abdominal PNBs and stress hormones in laparoscopic colorectal surgery. This new knowledge is very important in current settings where both surgery and anesthetic methods require low invasiveness in the perioperative period.

In this study, the total dose of iv-PCA fentanyl used in group L+PNBs was set 1/3 lower as compared to group H. The dose was determined by referring to the previous study¹⁷⁾. The dose used in group L + PNBs was focused on visceral pain that was not covered by abdominal PNBs. VAS scores were significantly lower at T3 in group L + PNBs. Although the difference in VAS between two groups was small (7.6/100), this suggests that group L + PNBs achieved better analgesia even if we reduced opioid analgesics. There were significantly fewer occurrences of PONV until T4 in group L + PNBs, demonstrating that reducing the opioid dose was advantageous. As a method for postoperative analgesia, the combination of abdominal PNBs with opioid analgesics may be of benefit in terms of reducing the opioid dose and lead to inhibition of PONV. Lower incidence of PONV until T4 in group L+PNBs may not be a direct effect of PNBs, but we believe that our finding that PONV could be suppressed while maintaining the quality of postoperative analgesia by combining PNBs and reducing fentanyl dose is clinically meaningful. The incidences of PONV were comparable between groups until T3, but at T4 were significantly higher in group H, so administration of fentanyl at a dose of 0.6 $\mu\text{g}/$

kg/h in group H after T3 may have been excessive. In further studies, using a PCA pump with a variable flow rate may allow appropriate doses of fentanyl to be set.

This study has several limitations. The first is that the study was single-blind, in that the medical staff were aware of the treatments administered. In order to establish more reliable evidence, additional studies will be needed. The second is that the VAS score, which was used as an indicator of the analgesic effect, was evaluated only when the patients were at rest. Previous reports have shown that, in a comparison with a non-block group, abdominal PNBs in laparoscopic surgery were less effective for relieving movement-related pain¹⁸⁾. Further, evaluations of pain relief should include movement-related pain in order to demonstrate the superiority of PNBs more accurately.

In conclusion, combining abdominal PNBs with opioid analgesics for postoperative analgesia in patients undergoing laparoscopic colorectal surgery is useful in terms of postoperative stress control and may be effective in relief of pain, reduction of opioid use, and inhibition of PONV. Abdominal PNBs could be an excellent method for postoperative analgesia in patients undergoing laparoscopic colorectal surgery.

Conflicts of interest: The authors have no conflict of interest to declare.

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腹腔鏡下大腸切除術後の
ストレス反応における超音波ガイド下
腹横筋膜面ブロック・腹直筋鞘ブロックの有用性

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要旨

腹腔鏡下大腸切除術を施行された患者において, 超音波ガイド下腹壁末梢神経ブロックとオピオイドの併用が術後ストレスホルモン及び臨床経過に与える効果を検討した. 85名の患者が組み込まれ, 術後鎮痛法別にオピオイド単独(H)群と神経ブロック併用(L + PNBs)群の二群にランダムに振り分けた. 血漿カテコラミン値(エピネフリン, ノルエピネフリン, ドパミン)と血清コルチゾール値を麻酔導入後(T1),

抜管前(T2), 術後第一病日朝(T3)の3回測定し, visual analog scale (VAS)値, 術後嘔気嘔吐(PONV)の発生も記録した. エピネフリン値とVAS値はT3においてL + PNBs群で有意に低く, 第三病日までのPONVはL + PNBs群で有意に少なかった. 腹腔鏡下大腸切除術の術後鎮痛において, オピオイドに腹壁末梢神経ブロックを併用することはストレスコントロールと鎮痛, PONV抑制の点で有用である.