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ORIGINAL ARTICLE

High-dose remifentanil suppresses stress response associated with pneumoperitoneum during laparoscopic colectomy

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Abstract
Purpose Although laparoscopic surgery is minimally invasive, it produces stress responses to an extent similar to that of conventional laparotomy. Both epidural anesthesia and remifentanil intravenously (i.v.), combined with general anesthesia, provide stable hemodynamics during laparoscopic surgery. However, it has not been elucidated whether epidural anesthesia and remifentanil are associated with suppression of autonomic and neuroendocrine stress responses. This study aimed to clarify whether thoracic epidural anesthesia (TEA) or remifentanil suppresses stress responses during laparoscopic surgery.
Methods We assigned 60 patients undergoing laparoscopic colectomy to three groups anesthetized with 40 % oxygen–air–sevoflurane plus either TEA (TEA group), continuous infusion of remifentanil 0.25 μg/kg/min [low-dose (LD) group], or 1.0 μg/kg/min [high-dose (HD) group] ($n = 20$ each group). Plasma concentrations of adrenocorticotropic hormone (ACTH), cortisol, antidiuretic hormone (ADH), and catecholamines were measured immediately before anesthesia induction, and 30 and 90 min after the start of pneumoperitoneum.
Results All groups showed no significant changes in hemodynamics during the course of anesthesia. Compared with TEA, both high-dose and low-dose remifentanil significantly suppressed increases in ACTH, ADH, and cortisol during pneumoperitoneum. Plasma adrenaline showed no significant changes during pneumoperitoneum in any group. Compared with TEA, low-dose remifentanil produced significantly higher plasma concentrations of noradrenaline and dopamine during pneumoperitoneum.
Conclusion Notwithstanding similar hemodynamic responses in all groups, only high-dose remifentanil suppressed both sympathetic responses and the hypothalamus–pituitary–adrenal axis. This result indicates that of these three anesthesia regimens, high-dose remifentanil seems most suited for laparoscopic surgery.

Keywords Opioids · Intravenous · Remifentanil · Laparoscopic surgery · Thoracic epidural anesthesia · Stress responses · Pneumoperitoneum

Introduction

Laparoscopic surgery has become a standard procedure in recent years. It is generally considered less stressful than conventional laparotomy, causing less pain and resulting in faster recovery and shorter hospitalization [1, 2]. Stress-induced deterioration in postoperative organ functions may be implicated in the development of postoperative complications. Modulation of stress responses to surgery may reduce postoperative morbidity and mortality [3]. Although laparoscopy is less invasive, laparoscopic maneuvers

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(including pneumoperitoneum), type of gases insufflated, and longer operating times still produce stress responses [4]. Indeed, some studies demonstrate intraoperative stress hormonal responses are similar in both laparoscopic and open laparotomic surgeries [5, 6]. One study demonstrated that thoracic epidural anesthesia (TEA) suppressed sympathoadrenal responses during laparoscopic cholecystectomy but did not affect the hypothalamus–pituitary–adrenocortical axis [7]. Opioids depress both the neuroendocrine axial responses to surgery [8, 9] and sympathetic activity [10, 11]. Furthermore, intravenous (i.v.) administration of remifentanil suppresses the release of adrenaline but not noradrenaline [11, 12]. These results indicate that epidural and remifentanil anesthesia suppress stress responses to laparoscopic surgery in different manners and to different degrees. This study aimed to investigate the effects of epidural and remifentanil anesthesia on the hypothalamus–pituitary–adrenocortical axis and sympathoadrenal responses to laparoscopic surgery. Two doses of remifentanil were used because remifentanil shows a dose-dependent suppression of sympathetic activity during laparoscopic surgery [10, 11].

Materials and methods

Patients

The protocol was approved by the Local Ethics Committee of Juntendo University Urayasu Hospital, and written informed consent was obtained from all patients before enrollment. Patients were aged between 20 and 80 years [American Society of Anesthesiologists (ASA) Physical Status (PS) 1–2] and were not using drugs known to affect sympathetic responses, such as monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors. Patients had no history of cardiovascular or autonomic nervous system diseases, severe diabetes, endocrine disorders, or obesity [body mass index (BMI) >30 kg/m^2]. Sixty patients scheduled for laparoscopic-assisted colectomy were assigned to three different groups by closed-envelope randomization; these groups received TEA ($n = 20$), high-dose remifentanil (HD; $n = 20$), or low-dose remifentanil (LD; $n = 20$).

Anesthesia

All patients were administered midazolam 0.03–0.1 mg/kg intramuscularly 1 h before anesthesia induction. A cannula was placed in the radial artery before induction for continuous arterial blood pressure monitoring and blood sampling. An epidural catheter was placed in the intervertebral space between T10 and T11 before anesthesia induction. In all groups, for the induction of general anesthesia, 1.0 mg/kg propofol was administered 3 min after starting the infusion of remifentanil at 0.5 μg/kg/min. Endotracheal intubation was facilitated with rocuronium (0.9 mg/kg), and the lungs were mechanically ventilated to maintain an end-tidal carbon dioxide tension between 35 and 45 mmHg, with a fraction of inspired oxygen (FIO_2) of 0.4. Additional doses of rocuronium were administered when train-of-four stimulation resulted in more than two contractions. Anesthesia was maintained by sevoflurane inhalation. The anesthesia level was controlled with the bispectral index (BIS) level kept between 40 and 60. Throughout the operation, patients received Ringer bicarbonate solution at a basal rate of 5–10 ml/kg/h.

In the TEA group, remifentanil infusion was discontinued immediately after intubation, and 1.0 % ropivacaine (1.0 mg/kg) was administered through the epidural catheter, followed by bolus doses of redundant ropivacaine (0.5 mg/kg) at 90-min intervals. In the HD group, the rate of the continuous remifentanil infusion was stepped down to 0.25 μg/kg/min immediately after intubation, increased to 1.0 μg/kg/min 5 min before the start of surgery, which was maintained throughout surgery. In the LD group, remifentanil dose was decreased to 0.25 μg/kg/min immediately after intubation and maintained throughout surgery. Doses of remifentanil were chosen based on previous reports by Weale et al. [13], in which remifentanil $\geq$1.0 μg/kg/min effectively suppressed increases of heart rate (HR) and plasma glucose levels during surgery; however, remifentanil 0.25 μg/kg/min did not suppress either.

At the end of pneumoperitoneum, 0.5 % ropivacaine (0.5 mg/kg) was administered through the epidural catheter, and patient-controlled epidural analgesia [a continuous infusion of 0.2 % ropivacaine (4 ml/h) with rescue dose of 3 ml, lockout intervals of 30 min] was started in all groups. In the TEA group, we identified the analgesic level by the presence of a cold sensation immediately after surgery. The upper level of anesthesia was between T2 and T6 in all patients. The maximum level of intraperitoneal pressure during laparoscopy was 12 mmHg. Patient body temperature was kept within normal limits.

Measurements

Mean arterial blood pressure (MAP) and HR were measured before induction of anesthesia (time 1), at the tracheal intubation (time 2), 5 min after intubation (time 3), at the start of pneumoperitoneum (time 4), 30 min after starting pneumoperitoneum (time 5), at the end of pneumoperitoneum (time 6), and at the end of surgery (time 7). Blood was sampled to measure plasma concentrations of

adrenocorticotropic hormone (ACTH), cortisol, antidiuretic hormone (ADH), and catecholamines (adrenaline, noradrenaline, and dopamine) before anesthesia induction (induction) and 30 min (P30) and 90 min (P90) after starting pneumoperitoneum. Cortisol and ADH concentrations were analyzed by radioimmunoassay. ACTH concentration was analyzed by electrochemiluminescence immunoassay. Catecholamine concentrations were measured by high-performance liquid chromatography (HPLC).

Statistical analysis

Sample size in each group was determined using power analysis. Marana et al. [9] compared plasma levels of stress hormones between total i.v. anesthesia (TIVA) and sevoflurane anesthesia. They demonstrated that when the difference in mean value of ACTH plasma level was approximately 200 pg/ml, the difference was significant between groups. Therefore, with an expected difference of 200 pg/ml in the between-group means, a standard deviation (SD) of 200 of the means, significance at the two-side 5 % level, and a power of 80 %, a sample size of 17 was necessary. Twenty patients were enrolled in each group to compensate for a possible dropout rate of 20 %. Data were expressed as mean ± SD, and statistical analysis was performed by one-way analysis of variance (ANOVA) for patient demographics or anesthetic variables and two-way ANOVA for hemodynamics, hormones, and catecholamines and Bonferroni's post hoc test. Statistics were calculated using the statistical software package GraphPad Prism (version 5.00; GraphPad Software, La Jolla, CA, USA).

Results

Surgery was completed uneventfully in all patients. There were no significant intergroup differences in patient demographics or anesthetic variables, except intraoperative urinary output. Urine output in the HD group was significantly greater than that in the TEA group (Table 1).

There were no differences in MAP among the three groups at any measurement points (Fig. 1a). Compared with the other groups, the TEA group presented significantly higher HR at times 4 and 5; however, within-group temporal changes in HR were not significant in any group (Fig. 1b).

Before anesthesia induction, there were no intergroup differences in plasma concentration of any hormone or catecholamine. In the HD and LD groups, plasma concentrations of ACTH and cortisol at P30 and P90 were significantly lower than at induction, and plasma concentration of ADH did not change from baseline. In contrast, in the TEA group, plasma concentrations of ACTH, cortisol, and ADH were significantly higher at P30 and P90 than at induction. During pneumoperitoneum, plasma concentrations of ACTH, cortisol, and ADH were significantly higher in the TEA group than in both the HD and LD groups (Fig. 2a–c).

Although adrenaline concentrations were significantly lower during pneumoperitoneum (P30 and P90) than before induction in all groups, there were no intergroup differences (Fig. 3a). In the TEA group, plasma concentrations of noradrenaline were significantly lower at P30 and P90 than at induction. However, changes in noradrenaline concentration were not significant in the HD and LD groups. Plasma concentrations of noradrenaline during pneumoperitoneum (P30 and P90) were significantly higher in the LD group than in the TEA group (Fig. 3b). In the HD and LD groups, plasma concentrations of dopamine were higher at P90 than at induction; they were also higher at P30 and P90 than at induction in the TEA group. However, plasma dopamine concentrations during pneumoperitoneum (P30 and P90) were significantly higher in the LD group than in the HD and TEA groups (Fig. 3c).

Table 1 Patient characteristics and anesthesia demographics

	Epidural anaesthesia (TEA)	High-dose remifentanil (HD)	Low-dose remifentanil (LD)
Age (years)	62.1 (10.4)	62.7 (10)	63.9 (12.1)
Sex (M/F)	14/6	9/11	12/8
Height (cm)	158.6 (7.9)	161.2 (7.4)	159.3 (7.5)
Body weight (kg)	56.9 (9.9)	60.9 (10.2)	60.2 (12.6)
Amount of intravenous fluid infusion (ml)	3,357 (1,090.6)	2,846.5 (873.5)	3,298.5 (1,206.9)
Blood loss (ml)	40.6 (50.5)	81.4 (145.0)	130.3 (156.1)
Duration of anesthesia (min)	261.5 (59)	263 (63)	281.4 (66)
Duration of surgery (min)	187.5 (50)	197.3 (66)	218.3 (74)
Duration of pneumoperitoneum (min)	130.1 (41)	148.5 (61)	154.9 (58)
Urine output (ml)	447 (243)	746 (478)*	604 (235)

Values are represented as mean (standard deviation)

M male, *F* female, *TEA* thoracic epidural anesthesia, *HD* high dose, *LD* low dose

* $P < 0.05$ compared with epidural anesthesia group

Discussion

The new findings of this study were that epidural anesthesia completely suppressed catecholamine release but not

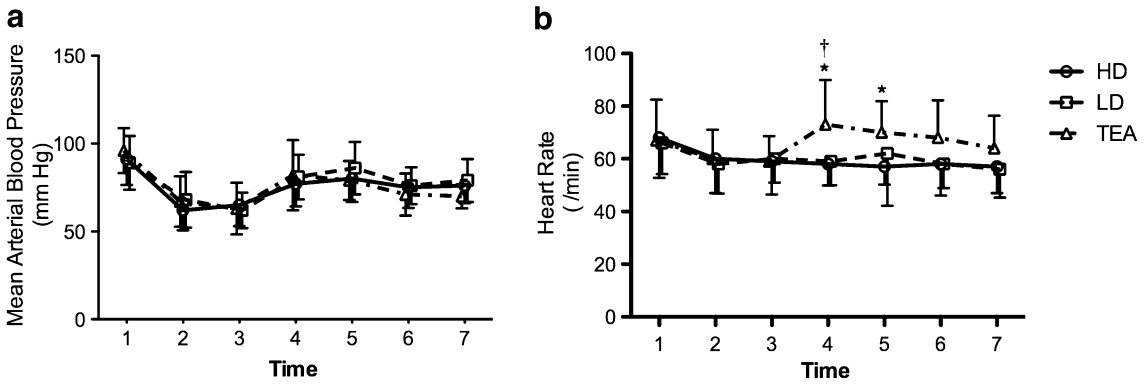

Fig. 1 Mean arterial blood pressure (**a**) and heart rate (**b**) in patients receiving high-dose remifentanil (HD), low-dose remifentanil (LD), and thoracic epidural (TEA) anesthesia. *Time numbers* on the abscissas indicate the following: *1* before anesthesia induction, *2* at tracheal intubation, *3* 5 min after tracheal intubation, *4* start of pneumoperitoneum, *5* 30 min after pneumoperitoneum, *6* end of pneumoperitoneum; *7* end of surgery. Values are shown as mean ± standard deviation. $^{*}P < 0.05$ HD compared with TEA. $^{\dagger}P < 0.05$ LD compared with TEA

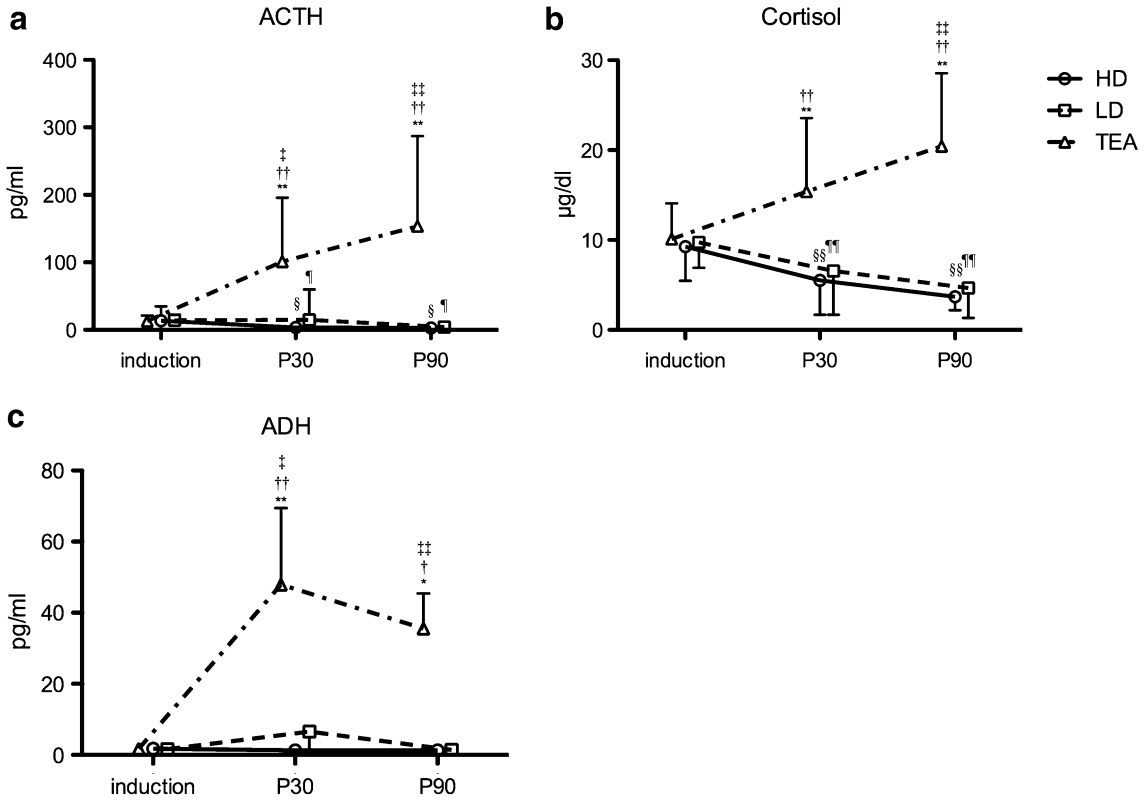

Fig. 2 Plasma concentrations of adrenocorticotropic hormone (ACTH) (**a**), cortisol (**b**), and antidiuretic hormone (ADH) (**c**) in patients receiving high-dose (HD), low-dose (LD), and thoracic epidural (TEA) anesthesia. Induction, P30, and P90, indicate before anesthesia induction, 30 min after pneumoperitoneum, and 90 min after pneumoperitoneum, respectively. Normal ranges of cortisol, ADH, and ACTH were 4.0–18.3 μg/dl, 0.3–3.5 pg/ml, and 7.2–63.3 pg/ml, respectively. Values are represented as mean ± standard deviation. $^{*}P < 0.05$ and $^{**}P < 0.01$, HD compared with TEA. $^{\dagger}P < 0.05$ and $^{\dagger\dagger}P < 0.01$, LD compared with TEA. $^{\S}P < 0.05$ and $^{\S\S}P < 0.01$ compared with induction in HD group. $^{\P}P < 0.05$ and $^{\P\P}P < 0.01$ compared with induction in LD group. $^{\ddagger}P < 0.05$ and $^{\ddagger\ddagger}P < 0.01$ compared with induction in TEA group

the neuroendocrine stress response and that remifentanil dose dependently inhibited sympathetic and neuroendocrine stress responses, despite both treatments exerting similar effects on cardiovascular responses. HR was significantly higher in patients receiving TEA than those receiving LD and HD remifentanil at the start of pneumoperitoneum and 30 min after starting pneumoperitoneum; however, temporal variations were insignificant.

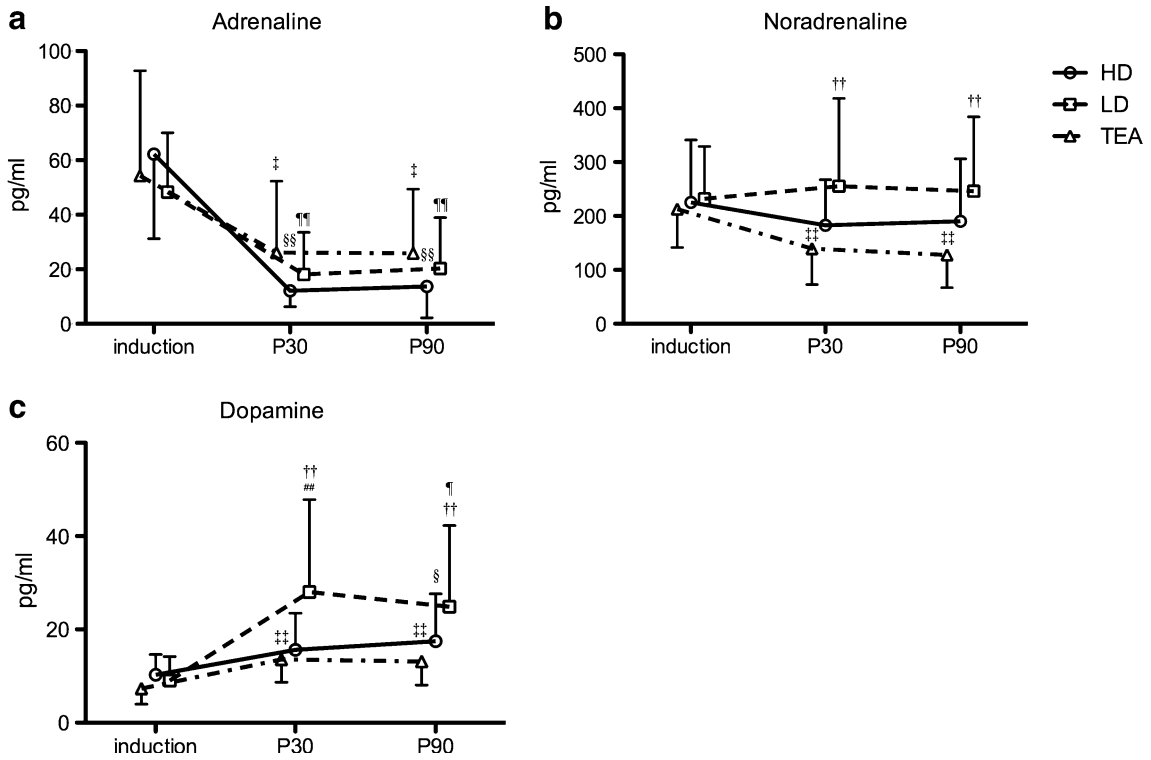

Fig. 3 Plasma concentrations of adrenaline (**a**), noradrenaline (**b**), and dopamine (**c**) in patients receiving high-dose (HD), low-dose (LD), and thoracic epidural (TEA) anesthesia. *Induction*, *P30*, and *P90* before anesthesia induction, 30 min after pneumoperitoneum, and 90 min after pneumoperitoneum, respectively. Normal ranges of adrenaline, noradrenaline, and dopamine were <100, 100–450, and <20 pg/ml, respectively. Values are represented as mean ± standard deviation. $^{\#\#}P < 0.01$ HD compared with LD. $^{\dagger\dagger}P < 0.01$ LD compared with TEA. $^{\S}P < 0.05$ and $^{\S\S}P < 0.01$ compared with induction in HD group. $^{\P}P < 0.05$ and $^{\P\P}P < 0.01$ compared with induction in LD group. $^{\ddagger}P < 0.05$ and $^{\ddagger\ddagger}P < 0.01$ compared with induction in TEA group

This suggests that the hemodynamics remained reasonably stable throughout the study in all groups. Regardless, both hypothalamus–pituitary–adrenal hormones and catecholamines showed different responses among the three groups.

Although TEA did not inhibit responses of ACTH, cortisol, and ADH, remifentanil 0.25 and 1 μg/kg/min suppressed the release of these hormones, indicating that remifentanil suppresses hypothalamic–pituitary–adrenal responses. These results resemble those obtained in previous studies. Several studies demonstrate that responses of these hormones were suppressed by administration of opioids and that TEA did not suppress the responses during laparoscopic surgery [3, 7, 9, 10, 14]. In contrast, Ahlers et al. [15] indicate that intraoperative TEA suppressed stress hormones in patients undergoing major abdominal surgery. Furthermore, Chae et al. [16] show that epidural anesthesia lowered the concentration of cortisol in patients undergoing open heart surgery. Although these results differ from our data, these discrepancies are likely due to the pneumoperitoneum during laparoscopy. Aono et al. [7] suggest that peritoneal stretching due to carbon dioxide (CO_2) pneumoperitoneum produced an intense noxious stimulus. Increased phrenic nerve activity due to peritoneal stretching may play an important role in the relay of afferent nociceptive neural information to the hypothalamus [17]. Failure to block this phrenic nerve activity by TEA might maintain the responses of pituitary hormones to pneumoperitoneal stimulation in this study. Kainuma et al. [18] demonstrated that an injection of hydrocortisone induced hypothermia, hyperglycemia, and immunomodulation in mice and that these responses were suppressed by administration of a glucocorticoid receptor antagonist. These results suggest that glucocorticoid is an important mediator of the stress response. In our study, remifentanil infusion, but not TEA, suppressed neuroendocrine hormones; this suggests that remifentanil, but not TEA, suppresses responses induced by surgical stress, including hypothermia, hyperglycemia, and immunomodulation. Also in this study, TEA completely suppressed the responses of catecholamines. However, LD remifentanil inhibited the response of adrenaline but not noradrenaline or dopamine. HD remifentanil inhibited increases in plasma concentrations of both adrenaline and dopamine and tended to attenuate noradrenaline release during pneumoperitoneum. These observations are similar to those of previous studies. TEA suppressed adrenaline and

noradrenaline releases during laparoscopic cholecystectomy [7]. LD fentanyl and remifentanil inhibited the release of adrenaline but not that of noradrenaline [7, 11, 19]. These findings may be due to the fact that different nerves are involved in catecholamine secretions. Both noradrenaline and dopamine are released from the adrenal medulla and sympathetic nerve endings [20, 21], whereas adrenaline is released from the adrenal medulla alone [10]. Adrenal medulla activity is modulated by presynaptic sympathetic fibers, which are activated centrally [7, 11]. On the other hand, peripheral sympathetic activations, such as spinal reflexes, elicit the release of noradrenaline and dopamine. Epidural anesthesia blocks the afferent sympathetic pathways, resulting in suppression of all three catecholamine-release mechanisms [7]. In contrast, central nervous system inhibition by remifentanil may suppress the release of adrenaline. Compared with central inhibition, peripheral sympathetic effects of remifentanil are weak and dose dependent [10, 11]; this may explain the differences in the release of noradrenaline and dopamine between HD and LD remifentanil in our study. Indeed, Myre et al. [11] demonstrate that a dose equivalent to LD remifentanil in this study was not sufficient to suppress responses of noradrenaline and dopamine. In contrast, 1.0 μg/kg/min of remifentanil (HD in our study) produced a predicted effect-site concentration of 24 ng/ml that may be sufficient to suppress the stress response.

Concentrations of hormones and catecholamines were measured only before and during pneumoperitoneum, which is one limitation of the study. Surgical responses lasting postoperatively affect postoperative recovery and even outcome. However, Ahlers et al. [15] demonstrate that suppression of the intraoperative stress response by epidural anesthesia attenuated stress-induced immunosuppression, which indicates that intraoperative stress response suppression is important. Therefore, our study focused on the effects of anesthesia on intraoperative stress response, particularly during pneumoperitoneum. Consequently, it is of value to examine whether TEA or remifentanil anesthesia affects postsurgical stress response, outcomes, or complications. Another limitation of our study is that the analgesic level before induction of general anesthesia was not measured in the TEA group. Rather, the level of epidural analgesia was examined only on emergence from anesthesia using a cold test. It is assumed that the intermediate amount of ropivacaine would not make a great difference in analgesia range.

In conclusion, this study shows that responses of the hypothalamic–pituitary–adrenal axis were suppressed by a continuous i.v. infusion of 1.0 μg/kg/min remifentanil during laparoscopic colectomy. Moreover, remifentanil suppressed not only the responses of adrenaline but also of dopamine and noradrenaline. These findings suggest that supplementation of general anesthesia with a continuous i.v. infusion of 1.0 μg/kg/min remifentanil is a suitable anesthesia technique for laparoscopic surgery.

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