ORIGINAL ARTICLE

A laparoscopic gastrectomy approach decreases the incidence and severity of emergence agitation after sevoflurane anesthesia

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Abstract

Purpose Compared to open gastrectomy (OG), laparoscopic gastrectomy (LG) has improved short-term outcomes and equivalent oncological outcomes. In this study, a potential short-term advantage of LG over OG, reduced risk of emergence agitation, was evaluated.

Methods This retrospective study compared LG versus OG with respect to emergence agitation in 400 adult patients who underwent sevoflurane anesthesia. In all cases, a serial Richmond Agitation–Sedation Scale (RASS) assessment was performed in the postanesthesia care unit (PACU). Patients with a RASS score $\geq +1$ at any time were considered to have emergence agitation. Severe agitation was defined as a RASS score of $+3$ or $+4$.

Results This study included 214 OG group subjects and 186 LG group subjects in the analysis. The overall incidence of emergence agitation was significantly lower in the LG group than the OG group (23.7 vs. 43.5 %, $p < 0.001$). The LG group had a significantly lower incidence of severe agitation than the OG group (1.1 vs. 4.7 %, $p = 0.035$). Multivariate logistic regression analysis demonstrated that the type of surgery (OG vs. LG), as well as current smoking, total dose of rescue opioids used in the PACU, and maximum pain score in the PACU, were independent risk factors for emergence agitation (odds ratio, 1.984; 95 % confidence interval, 1.249–3.153; $p = 0.004$). Patients with emergence agitation had significantly increased PACU stays ($p = 0.024$).

Conclusions Compared to an open approach, a laparoscopic gastrectomy approach can provide the short-term benefit of decreased emergence agitation.

Keywords Anesthesia recovery period · Gastrectomy · Laparoscopy · Psychomotor agitation

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Introduction

Emergence agitation is defined as a disturbance in a patient's awareness of and attention to his/her environment with disorientation and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behavior in the immediate postanesthesia period [1]. Severe episodes of emergence agitation may not only cause injury to the patients or to the surgical site but may also cause medical staff injuries. As a result, emergence agitation may increase physical, psychological, and financial burdens in the postanesthesia care unit (PACU) [2]. Furthermore, previous studies [3, 4] suggest that emergence agitation in the PACU is associated with a higher incidence of postoperative delirium during subsequent hospitalization.

Abdominal surgeries, such as gastrectomy, have a higher incidence of emergence agitation [2, 5]. This is probably due to severe postoperative pain and a sense of breathing difficulty during emergence from anesthesia. Laparoscopic gastrectomy (LG) has better short-term outcomes (i.e., less postoperative pain, earlier functional recovery, and fewer postoperative respiratory complications) compared to open gastrectomy (OG) [6]. Thus, we

hypothesized that LG could protect patients from developing emergence agitation when compared to OG.

In this retrospective study, the incidence and severity of emergence agitation following LG and OG were compared in adult patients who underwent sevoflurane anesthesia for gastric cancer resection. In addition, we examined whether the type of surgery (OG vs. LG) was an independent risk factor for emergence agitation.

Methods

With the approval of the Institutional Review Board (IRB file no.: 2014-03-067, approval date: April 7, 2014), we retrospectively examined the records of 400 patients aged ≥18 years who underwent sevoflurane anesthesia for elective LG (LG group, $n = 186$) or OG (OG group, $n = 214$) for gastric cancer resection from November 2012 to January 2014 at our institution. LG procedures included both laparoscopy-assisted gastrectomy (LAG) and totally laparoscopic gastrectomy (TLG). In the LG group, 75 cases were LAGs and 111 TLGs.

Because the presence of tracheal tube in the PACU [2, 5] and supplemental remifentanil infusion [7] could influence the incidence of emergence agitation, the following patients were excluded: patients who were not extubated on arrival in the PACU or those received supplemental remifentanil infusion during surgery. Patients admitted directly to the intensive care unit (ICU) were also excluded.

In our institution, serial Richmond Agitation–Sedation Scale (RASS) assessments [8] (on admission to the PACU and every 10 min thereafter) have been routinely performed for every patient admitted to the PACU following general anesthesia since 2011. However, RASS data obtained before November 2012 were not included in this study to allow the surgeons to become familiar with the LG procedures. The RASS is a ten-point scale with four levels that indicate agitation, one level that denotes a calm and alert state, and five levels for sedation. Our institution's clinical protocol encourages PACU nurses and physicians to target a RASS score of 0 ("alert and calm") in all patients. Patients in the PACU with a RASS ≥+1 at any time were classified to have emergence agitation. For patients with emergence agitation, we also noted the highest RASS score while in the PACU. Severe agitation was defined as a RASS score of +3 or +4, and in those cases physical restraints were applied or midazolam was administered.

Anesthetic techniques were similar in all cases. Without premedication, anesthesia was induced by intravenous (IV) propofol or thiopental and rocuronium. Anesthesia was maintained with sevoflurane and 50 % oxygen. Muscle relaxation was maintained by IV vecuronium (0.02 mg/kg)

at regular intervals. An IV opioid (meperidine, hydromorphone, or fentanyl) was routinely given 30 min prior to the end of surgery to control postoperative pain. After completion of surgery, reversal of residual neuromuscular block was achieved, and the tracheal tube was removed in the operating room.

Two experienced surgeons, familiar with both OG and LG, who had performed more than 100 of each procedure, conducted all of the surgical procedures described in this study. While a 25–30-cm-long upper median skin incision was made for OG, a 4–5-cm midline incision in the epigastrium (LAG) or vertical incision in the infraumbilical port site (TLG) was made for LG. At our institution, the surgical indication for both laparoscopic procedures was the same: pre-operative stage $T_{1-2}N_{0-1}$ gastric cancer.

In the PACU, all patients were managed using the following standardized postoperative protocols: (1) serial assessments of pain with an 11-point numerical rating scale (NRS), and emergence agitation by RASS, at admission, every 10 min thereafter, and at discharge from the PACU; (2) application of IV patient-controlled analgesia (PCA) using ketorolac and fentanyl, and rescue analgesic administration of meperidine or hydromorphone in patients with a pain NRS score ≥5; (3) antiemetic treatment with IV ramosetron or granisetron in patients with intolerable postoperative nausea and vomiting (PONV); and (4) PACU discharge criteria based on a modified Aldrete score (scores of 9 or greater were deemed appropriate for discharge).

The following variables were also noted for each patient: demographic data, American Society of Anesthesiologists (ASA) physical status, current smoking (smoked within 1 week of surgery and smoked at least ten cigarettes per day for more than 1 year), alcohol abuse (average 3–4 drinks per day four or more times per week), history of previous general anesthesia, educational level, duration of surgery and anesthesia, minimum alveolar concentration-hours (MAC-h), intraoperative use of anticholinergics, total doses of opioids used for postoperative pain in the operating room and PACU, tympanic temperature on PACU admission, pain NRS scores, presence of PONV requiring antiemetics in the PACU, and length of PACU stay. All opioid administrations were converted to IV morphine equivalent doses [9]. MAC-h was calculated (average MAC × length of exposure) as an index of anesthetic exposure.

Statistical analyses were performed using SPSS software (ver. 18.0, SPSS Inc., Chicago, IL, USA). First, the incidence of emergence agitation was compared between the OG and LG groups, and then other univariate characteristics of patients with and without emergence agitation were compared using unpaired t or χ^2 tests. Second, a backward stepwise multivariate logistic regression analysis was conducted to determine whether the type of surgery (OG

vs. LG) was an independent risk factor for emergence agitation. Variables with a p value ≤ 0.2 in the univariate analysis were entered into a logistic regression model. Goodness-of-fit was evaluated using the Hosmer–Lemeshow test. Independent risk factors are expressed as odds ratio (OR) with 95 % confidence intervals (CI). Statistical significance was set at $p < 0.05$.

Results

Table 1 shows demographic, operative, anesthetic, and PACU data of the OG and LG groups. Whereas the OG group had an older age and increased intraoperative blood loss, the LG group had a higher MAC-h, a higher proportion of PONV requiring antiemetics, and less postoperative pain (a lower maximum pain NRS score and a reduced dose of rescue opioids in the PACU).

The overall incidence of emergence agitation was significantly lower in the LG group than the OG group [23.7 % (44/186) vs. 43.5 % (93/214)]. Regarding severe

Table 1 Comparison of clinical characteristics between the open gastrectomy (OG) and laparoscopic gastrectomy (LG) groups

	OG group ($n = 214$)	LG group ($n = 186$)	p value
Gender: female/male	82/132	87/99	0.108
Age (year)	56.8 ± 11.3	52.3 ± 10.2	$<0.001^*$
Current smoking: yes/no	69/145	48/138	0.193
Alcohol abuse: yes/no	37/177	29/157	0.748
Height (cm)	163.4 ± 8.2	163.5 ± 8.9	0.840
Weight (kg)	63.5 ± 10.3	64.0 ± 10.7	0.647
BMI (kg/m^2)	23.7 ± 3.1	23.8 ± 2.7	0.796
ASA physical status: I/I/III	80/106/48	64/79/43	0.302
MAC-h (h)	4.7 ± 1.3	5.2 ± 1.4	0.001^*
EBL (ml)	135.7 ± 84.3	95.7 ± 69.4	$<0.001^*$
Duration of surgery (min)	126.9 ± 29.5	129.8 ± 32.6	0.354
Duration of anesthesia (min)	158.0 ± 30.1	163.7 ± 33.4	0.076
Total dose of opioids used for postoperative pain (morphine equivalents, mg)			
In the operating room	4.6 ± 0.7	4.5 ± 0.4	0.376
In the PACU	6.8 ± 3.1	5.5 ± 2.4	$<0.001^*$
Maximum pain NRS score in the PACU (0–10)	7.7 ± 1.6	7.3 ± 1.7	0.008^*
PONV requiring antiemetics: yes/no	6/208	17/169	0.012^*

Data are presented as mean $\pm$ SD or numbers

BMI body mass index, *ASA* American Association of Anesthesiologists, *MAC-h* minimum alveolar concentration-hours, *EBL* estimated blood loss, *PACU* postanesthesia care unit, *NRS* numerical rating scale, *PONV* postanesthesia nausea and vomiting

* Statistically significant difference ($p < 0.05$)

emergence agitation, the LG group had a significantly lower incidence than the OG group [1.1 % (2/186) vs. 4.7 % (10/214)] (Fig. 1). However, all patients regained normal cognitive status before discharge from the PACU.

To select candidates for logistic regression analysis, other univariate characteristics between patients with and without emergence agitation were compared. In addition to the type of surgery, the following seven variables were found to be significantly associated with emergence agitation (at $p \leq 0.2$): gender, current smoking, alcohol abuse, EBL, total dose of rescue opioids used in the PACU, maximum pain NRS score in the PACU, and PONV requiring antiemetics (Table 2).

Multivariate logistic regression demonstrated that the type of surgery (OG vs. LG) was an independent risk factor for emergence agitation (Table 3). Similar to the type of surgery, current smoking nearly doubled the risk of emergence agitation. The following two factors were also found to be significantly associated with emergence agitation: total dose of rescue opioids used in the PACU and the maximum pain NRS score in the PACU (Table 3).

Finally, the mean length of PACU stay was significantly longer for agitated patients than non-agitated patients (Table 2).

Discussion

The present study found that the type of surgery (OG vs. LG) was found to be an independent risk factor of emergence agitation. This finding may be mainly attributed to differences in postoperative pain. Such an explanation is
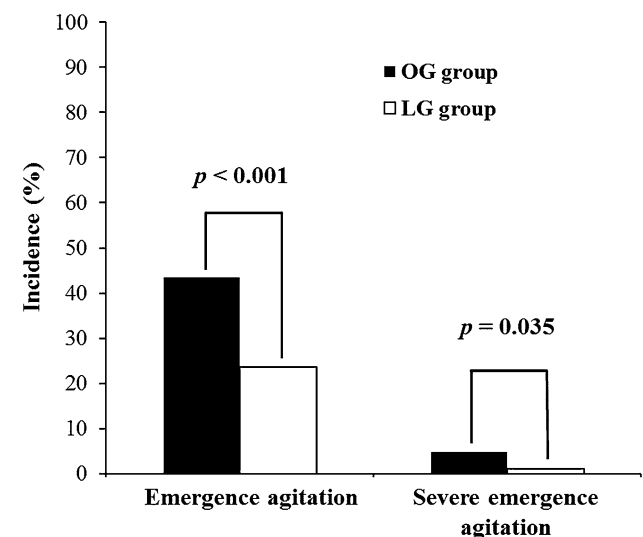

Fig. 1 Incidences of overall emergence agitation and severe emergence agitation in the open gastrectomy (OG) and laparoscopic gastrectomy (LG) groups

Table 2 Univariate analyses of agitated and non-agitated patients

	Non-agitated (n = 263)	Agitated (n = 137)	p value
Type of surgery: open/laparoscopic	121/142	93/44	<0.001*
Gender: female/male	122/141	47/90	0.027*
Age (year)	54.4 ± 10.5	55.4 ± 11.9	0.392
Current smoking: yes/no	63/200	54/83	0.002*
Alcohol abuse: yes/no	37/226	29/108	0.094
History of previous GA: yes/no	117/146	60/77	0.760
Education level: less than middle school/middle or high school/college graduate	34/118/111	15/68/54	0.647
BMI (kg/m²)	23.8 ± 2.9	23.7 ± 3.1	0.746
ASA physical status: I/I/III	78/128/57	46/57/34	0.405
Intraoperative use of anticholinergics: yes/no	54/209	34/103	0.393
EBL (ml)	111.6 ± 80.2	127.6 ± 79.4	0.059
MAC-h (h)	5.0 ± 1.4	4.9 ± 1.3	0.894
Duration of surgery (min)	128.0 ± 30.9	128.7 ± 31.2	0.822
Duration of anesthesia (min)	162.6 ± 32.6	161.6 ± 31.9	0.754
Time from end of surgery to extubation (min)	3.3 ± 2.5	3.2 ± 2.0	0.609
Total dose of opioids used for postoperative pain (morphine equivalents, mg)			
In the operating room	4.6 ± 0.6	4.5 ± 0.3	0.278
In the PACU	5.7 ± 2.6	7.2 ± 3.2	<0.001*
Maximum pain NRS score in the PACU (0–10)	7.2 ± 1.4	8.2 ± 1.9	<0.001*
PONV requiring antiemetics: yes/no	19/244	4/133	0.126
Core temperature: <36.0 °C/36.0–37.5 °C/>37.5 °C	93/170/0	56/81/0	0.330
PACU stay time (min)	69.7 ± 12.2	73.1 ± 15.2	0.024*

Data are presented as mean ± SD or numbers

GA general anesthesia, *BMI* body mass index, *ASA* American Association of Anesthesiologists, *EBL* estimated blood loss, *MAC-h* minimum alveolar concentration-hours, *NRS* numerical rating scale, *PACU* postanesthesia care unit, *PONV* postanesthesia nausea and vomiting

* Statistically significant difference ($p < 0.05$)

Table 3 Logistic regression analysis: independent risk factors of emergence agitation

Variable	OR	95 % CI	p value
Maximum pain NRS score in the PACU (0–10)	1.415	1.208–1.658	<0.001
Total dose of rescue opioids used in the PACU (morphine equivalents, mg)	1.118	1.024–1.221	0.013
Recent smoking	2.074	1.284–3.350	0.003
Type of surgery: open vs. laparoscopic	1.984	1.249–3.153	0.004

OR odds ratio, *CI* confidence interval, *NRS* numerical rating scale, *PACU* postanesthesia care unit

small, although statistically significant. Thus, other operative factors might have affected the results. This assumption is supported by a previous study, which found that emergence agitation was observed even in the absence of postoperative pain [10].

Several studies demonstrated that emergence agitation in the PACU is closely associated with subsequent delirium in ward [3, 4]. In this regard, surgical stress and inflammatory response may play important roles in the pathogenesis of emergence agitation. Regarding postoperative delirium, experimental [11] and clinical [12] studies have suggested that surgical trauma results in increased levels of inflammatory cytokines and cortisol in the peripheral and central nervous system which impairs cognitive function. Theoretically, LG causes less surgical trauma and a subsequently decreased inflammatory response compared to OG. A previous randomized study [13] showed that the serum interleukin-6 level was significantly lower in LG patients compared to OG patients immediately after the surgery. Especially, in contrast to this previous study, the operative times in the present study were similar in both groups, which might augment the less-invasive property of LG. Therefore, the reduced surgical trauma and subsequent reduction in inflammation in the LG group might lead to a decreased incidence of emergence agitation. However, further study using inflammatory biomarkers is needed to clarify the importance of the systemic inflammatory response in the pathogenesis of emergence agitation.

In addition, the surgical site might influence the risk of emergence agitation. Operations involving incisions near the diaphragm cause a reduction in vital capacity and limited diaphragmatic motion [14], resulting in a sense of breathing difficulty or suffocation during emergence from anesthesia. This phenomenon may cause emergence agitation. Severe pain with every respiration in the OG group could intensify agitated behaviors.

It is generally accepted that emergence agitation is the result of a complex interplay of patient vulnerability and

supported by a strong association of "total dose of rescue opioids used in the PACU" with emergence agitation in this study. It is clear that LG causes less postoperative pain than OG, which requires a large abdominal incision [6]. In addition, pain is a well-established risk factor for emergence agitation [1, 2, 5].

However, in the present study, the difference in the maximum pain NRS between the groups was somewhat

many precipitating factors. In order to find out what was linked to emergence agitation, we analyzed various potential factors. As a result, current smoking, as well as two postoperative pain-related variables (total dose of rescue opioids and the maximum pain NRS score in the PACU), were additionally identified as independent risk factors. To date, only one study [1] evaluated this issue and found a negative relationship between smoking habits and emergence agitation. However, unlike our study, that study included various surgical procedures and anesthetic techniques (total intravenous anesthesia and inhalational anesthesia with sevoflurane, desflurane, and isoflurane). The findings of the present study may reflect either a withdrawal agitation due to the abrupt cessation of nicotine consumption, or a direct neurotoxic effect of tobacco on the brain that diminishes the adaptive function to stressful situations.

In contrast to the previous study [2], male gender was not identified as an independent risk factor in this study. In that study, male gender was found to be one of the strong independent risk factors of emergence agitation. The most likely reason for this difference is the different study cohorts (gastrectomy only vs. various surgical procedures including abdominal surgery).

Several criticisms of the present study may be raised. First, the inclusion of multiple raters for RASS assessments may result in inconsistency within the RASS data. However, RASS demonstrated excellent inter-rater reliability, and criterion and construct validity [9]. Since routine use of RASS was implemented in our hospital, all PACU nurses have been provided with instruction for performing RASS assessments. Therefore, we do not believe the quality of the RASS data is hindered by multiple raters.

Second, although many perioperative variables were collected retrospectively, we were unable to assess how patient vulnerability (e.g., temperament or preoperative anxiety) influenced emergence agitation. Though adult data on this issue are limited, previous research studied for the U.S. military combat veteran surgical population demonstrated a positive relationship between emergence agitation and the amounts of anxiety, post-traumatic stress disorder symptoms, and depression [15]. However, the relatively large number of participants in the present study limits the influence such confounding factors have on the overall results.

Third, concern for the association between the extent of anesthetic exposure and emergence agitation may be raised. Thus, MAC-h values were compared between non-agitated and agitated patients, but these values were similar in both groups. This result is consistent with that of another study, in which there was no significant correlation between the hypnotic depth or duration of anesthesia and the incidence of emergence agitation [16].

Lastly, the mix-up of LAG and TLG techniques in the LG group may be a weak point of this study. However, recent meta-analysis demonstrates that these two techniques lead to similar postoperative pain and inflammatory response [17]. In this study, selection of LAG or TLG was based only on the surgeon's preference, independent of the patient's constitution or the location of the cancer. Thus, both techniques may lead to a similar risk of emergence agitation.

In conclusion, compared to an open approach, a laparoscopic approach significantly reduced the incidence and severity of emergence agitation in gastric surgical patients. In particular, the type of surgery (OG vs. LG) was found to be an independent risk factor of emergence agitation. Thus, selection of a laparoscopic approach can provide the short-term benefits of decreased emergence agitation and a shortened PACU stay to gastric surgery patients as soon as they leave the operating room.

Conflict of interest Nothing to declare.

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