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ORIGINAL ARTICLE

Effects of epidural anesthesia on postoperative nausea and vomiting in laparoscopic gynecological surgery: a randomized controlled trial

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Abstract

Purpose Patients undergoing laparoscopic gynecological surgery are susceptible to postoperative nausea and vomiting (PONV). We hypothesized that a combination of epidural and general anesthesia to minimize intraoperative opioid administration would reduce the incidence of PONV following laparoscopic gynecological surgery.

Methods Women undergoing elective laparoscopic gynecological surgery were randomly assigned to receive general anesthesia alone (group G, $n=45$) or general anesthesia with epidural anesthesia (group GE, $n=45$). Patients in group G received fentanyl and remifentanil for intraoperative analgesia, and those in group GE received single-shot ropivacaine at the time of induction of anesthesia. The primary outcome was the incidence of PONV within 24 h of surgery. Secondary outcomes included the use of rescue metoclopramide within 24 h of surgery and the time to first incidence of PONV and first use of rescue metoclopramide.

Results The incidence of PONV within 24 h of surgery was 60.0% in group G and 44.4% in group GE [relative risk (RR): 0.53, 95% confidence interval (CI): 0.23–1.23, $p=0.14$]. There were no intergroup differences in the use of rescue metoclopramide (40.0% in group G, 24.4% in group GE, RR: 0.49, 95% CI 0.20–1.20, $p=0.11$) and the time to first incidence of PONV and first use of rescue metoclopramide ($p=0.20$ and 0.12, respectively).

Conclusion Minimizing intraoperative opioid administration by combining epidural and general anesthesia did not reduce the 24-h incidence of PONV or rescue metoclopramide use after laparoscopic gynecological surgery.

Keywords Postoperative nausea and vomiting · Laparoscopic surgery · Gynecological surgery · Epidural anesthesia

Background

Laparoscopic surgery offers many advantages over open surgery, including smaller incisions, shorter postoperative recovery times, and better cosmetic results [1]. However, laparoscopic surgery is known to be associated with postoperative nausea and vomiting (PONV) [2]. Women undergoing laparoscopic gynecological surgery are particularly susceptible to PONV, with the reported incidence being as high as 70–85% [3–5]. Although PONV is rarely life-threatening, it is a major concern in surgical patients [6]; thus, adequate strategies for PONV reduction are essential.

For patients who are at a high risk of PONV, multiple interventions, including the prophylactic use of antiemetics and reduction of baseline risks, are recommended to prevent PONV [7]. However, some of the recommended antiemetics are unavailable or expensive, and most are not approved for prevention of PONV in Japan. Notably, minimization of intraoperative opioid use has been shown to decrease PONV after some surgical procedures [8–10], although this may result in intense postoperative pain following laparoscopic surgery [11]. To achieve adequate perioperative analgesia with minimum opioid administration, it might be necessary to use another anesthetic technique, such as neuraxial anesthesia, in combination with general anesthesia. Although

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avoidance of general anesthesia using regional anesthesia is one of the strategies used to reduce the baseline risk of PONV [7], it is not known whether a reduction in intraoperative opioid use using regional anesthesia would help reduce the incidence of PONV. We hypothesized that the concomitant use of epidural and general anesthesia to minimize intraoperative opioid use would reduce PONV and improve postoperative pain in patients undergoing laparoscopic gynecological surgery. The primary outcome was the incidence of PONV (any episode of nausea or vomiting) within 24 h of surgery, with the time of extubation defined as time 0. Secondary outcomes included the use of rescue metoclopramide within 24 h of surgery and the time to first incidence of PONV and first use of rescue metoclopramide. The total amount of rescue analgesics administered within 24 h of surgery was also examined.

Methods

Patients

This randomized controlled clinical trial was approved by the ethics committee at Tokyo Saiseikai Central Hospital on April 19, 2013 (approval number 293). The study was registered in the University Hospital Medical Information Network Clinical Trials Registry on April 30, 2013 (ID UMIN000010617). Women who were at least 18 years of age, undergoing elective laparoscopic gynecological surgery for a benign indication with an American Society of Anesthesiologists physical status (ASA PS) classification of I–II, and had two or more risk factors according to the simplified Apfel score [12] were eligible for inclusion in the study. Patients were excluded if they had contraindications to any of the study drugs or to epidural anesthesia, had taken emetogenic or antiemetic drugs within 24 h of surgery, had undergone emergency surgery, or were pregnant or lactating.

Randomization

After obtaining written informed consent, patients were randomly assigned to one of two study groups using a computer-generated random number table. The patients were evenly assigned to either study group. Patients in group G received general anesthesia alone and those in group GE received general anesthesia combined with epidural anesthesia. Sealed envelopes containing the group allocation were sequentially numbered and opened when the patient arrived in the operating room by a resident who was not involved in the study. Considering the nature of the study intervention, full blinding was not possible. However, the investigator who analyzed the data was blinded to group assignment and was not involved in the postoperative assessments.

Study intervention

All patients received anesthesia according to the standardized protocol, which consisted of intravenous (i.v.) fentanyl (100 μg) and propofol (2 mg/kg) for induction of anesthesia and sevoflurane in a mixture of 30–40% oxygen for maintenance of anesthesia. Before induction of general anesthesia, all patients received 8 mg of i.v. dexamethasone for PONV prophylaxis. No other antiemetics were administered during anesthesia. After induction of anesthesia, tracheal intubation was facilitated with rocuronium (0.6 mg/kg), and the lungs were mechanically ventilated to maintain an end-tidal CO_2 level of 35–45 mmHg during surgery. The amount of sevoflurane delivered was adjusted to maintain a bispectral index of 40–60. Neuromuscular blockade was maintained by intermittent administration of rocuronium 10 mg. At the end of the surgery, the residual neuromuscular blockade was reversed with sugammadex (4 mg/kg). A gastric tube was inserted during surgery and removed after aspiration of gastric contents at the conclusion of the procedure. In group G, intraoperative analgesia was provided by intermittent administration of fentanyl 25–50 μg and an infusion of remifentanil at 0.1–0.5 μg/kg/min. In group GE, 12–15 mL of ropivacaine 0.5% was injected at induction of anesthesia via an epidural catheter inserted between T11 and T12. No other opioids were administered intraoperatively. Postoperative epidural analgesia was started at the end of the surgery using ropivacaine 0.2% via a disposable elastomeric infusion pump (COOPDECH Balloonjector; Daiken Medical, Osaka, Japan) with an injection rate of 4 mL/h and was continued for 12 h. The epidural catheter was removed on the morning of the first postoperative day. If the patient's blood pressure decreased by ≥ 20% from the baseline value, ephedrine (4 mg) was administered.

After extubation, patients were transferred to the postanesthetic care unit (PACU) where they remained for at least 15 min. When patients left the PACU, they were asked by trained nursing staff to rate the worst episode of nausea they had experienced during their PACU stay using the following numeric rating scale (NRS): 0 = none, 1 = mild, 2 = moderate, and 3 = severe/intolerable [8]. When the NRS score for nausea was ≥ 1, the patient was considered to have nausea. The number of vomiting episodes was also recorded, with retching counting as a vomiting episode. The patient was considered to have PONV when the NRS score for nausea was ≥ 1 or episodes of vomiting were recorded. Metoclopramide 10 mg and fentanyl 25–50 μg were administered to treat PONV and postoperative pain, respectively, upon patient request. Patients were transferred to the main ward when their Aldrete score [13] reached ≥ 9 and they no longer required rescue analgesics.

At 2, 12, and 24 h postoperatively, each patient was asked by a trained ward nurse to rate the worst episode of nausea using the NRS and about the number of vomiting episodes during the preceding interval. Established PONV was treated with metoclopramide 10 mg at the patient's request. Postoperative pain was treated with a 50-mg indomethacin suppository or oral mefenamic acid (500 mg), also at the patient's request. Other analgesics, including oral acetaminophen (400 mg), intramuscular pentazocine (30 mg), and i.v. flurbiprofen (50 mg), were administered at the gynecologist's discretion.

Outcomes

The primary outcome was the incidence of PONV within 24 h of surgery. Secondary outcomes were the use of rescue metoclopramide within 24 h of surgery, the time to the first incidence of PONV and the first use of rescue metoclopramide, and the total amount of rescue analgesics administered within 24 h of surgery. Intraoperative and postoperative adverse events (e.g., failed sensory block, dural puncture, postoperative hypotension requiring treatment, urinary retention, paresthesia, and delayed ambulation) were recorded.

On the second postoperative day, each patient was asked to complete a questionnaire containing the following questions: Q1, Are you satisfied with the degree of nausea after surgery? Q2, Are you satisfied with the management of your postoperative pain? Q3, If you were to have the same surgery in the future, will you select the same type of anesthesia? Patients answered the questions using the following 5-point scale to rate postoperative nausea (question Q1) and pain (question Q2): 1 = very satisfied, 2 = satisfied, 3 = neutral, 4 = dissatisfied, 5 = very dissatisfied. For anesthesia preference (question Q3), patients used the following 5-point rating scale: 1 = very likely, 2 = likely, 3 = neutral, 4 = unlikely (if there is another technique), 5 = very unlikely (if there is another technique). Data were collected by resident physicians who were not involved in the study.

Statistical analyses

A power analysis was performed using a power of 80% and an α of 0.05. Given our retrospective observation that 61% of patients who received general anesthesia developed PONV within 24 h after surgery, we assumed that the incidence of PONV within 24 h of surgery in group G would be approximately 60%. We considered that a 30% reduction in the absolute risk of PONV would be clinically relevant. The power analysis showed that 42 patients were needed in each group. Allowing for possible dropouts, we allocated 45 patients to each group. The data analysis was based on an intention-to-treat population, which included all randomized participants who underwent surgery. Differences in the mean baseline patient characteristics (including age and body mass index) and surgery/anesthesia-related variables (including duration of surgery, intraoperative use of fentanyl and remifentanil, amount of ephedrine and fluids administered intraoperatively, and duration of PACU stay) were tested for statistical significance using the Student's *t* test. Differences in ASA PS classification, number of Apfel risk factors, proportion of non-smokers, history of PONV or motion sickness, incidence of PONV, nausea, and vomiting, use of rescue metoclopramide, and number of patients who received rescue analgesics were compared using chi-squared or Fisher's exact tests, as appropriate. Kaplan–Meier estimations of the time to PONV and first rescue metoclopramide use were prepared, with data censored to 24 h in cases where no PONV event and rescue metoclopramide use occurred. The amount of analgesics used, patient satisfaction with nausea and pain, and preferred method of anesthesia were compared using the Mann–Whitney *U* test. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using SPSS Version 22 (IBM Corp., Armonk, NY, USA).

Results

Ninety of the 143 eligible patients were randomized into the study. In group GE, postoperative epidural analgesia was not achieved in one patient because of failure of the epidural pump, and one patient received postoperative epidural fentanyl because of conversion to laparotomy; however, all patients were included in the intention-to-treat analysis. There were no differences in age, body mass index, ASA PS, number of Apfel risk factors, proportion of non-smokers, history of PONV and motion sickness, duration of surgery, or amount of intraoperative ephedrine and fluids used between the study groups (Table 1). All patients in group GE received fentanyl 100 μg to induce anesthesia, but no fentanyl or remifentanil was administered during surgery. All epidural blocks were successfully performed without dural puncture. The duration of stay in the PACU was significantly shorter in group GE than in group G ($p = 0.001$).

The incidences of postoperative PONV, nausea, and vomiting in the two groups are shown in Table 2. The overall incidence of PONV within 24 h of surgery was not significantly different between the study groups ($p = 0.14$). The incidences of nausea and vomiting were also not significantly different between the two groups. No significant intergroup difference was observed in the use of rescue metoclopramide ($p = 0.11$). Kaplan–Meier analysis of the time to the first incidence of PONV (Fig. 1a) and the time to the first use of rescue metoclopramide (Fig. 1b) showed no significant separation of the curves for groups G and GE ($p = 0.20$ and 0.12, respectively). Because several

Table 1 Baseline values and surgery/anesthesia-related variables

	Group G ($n=45$)	Group GE ($n=45$)	p value
Age, years	40.9 ± 9.2	42.5 ± 9.1	0.33[a]
BMI, kg/m^2	22.1 ± 3.6	21.4 ± 3.1	0.29[a]
ASA PS, I:II	38:7 (84.4:15.6)	36:9 (80.0:20.0)	0.78[b]
Number of apfel risk factors, 2:3	31:14 (68.9:31.1)	32:13 (71.1:28.9)	0.81[c]
Non-smoker	42 (93.3)	43 (95.6)	
History of PONV	0 (0.0)	4 (8.9)	
History of motion sickness	16 (35.6)	13 (28.9)	
Duration of surgery, min	154.1 ± 85.3	160.4 ± 101.5	0.77[a]
Intraoperative fentanyl, μg	487.8 ± 190.0	100.0 ± 0.0	< 0.001[a]
Intraoperative remifentanil, μg	1732 ± 1060	0.0 ± 0.0	< 0.001[a]
Intraoperative ephedrine, mg	15.1 ± 12.7	22.2 ± 21.0	0.21[a]
Intraoperative fluids, mL	1305 ± 593	1360 ± 623	0.87[a]
Duration of PACU stay, min	21.6 ± 10.2	16.1 ± 3.2	0.001[a]

Values are expressed as the mean ± standard deviation or number (%)

G general anesthesia, *GE* general anesthesia combined with epidural anesthesia, *BMI* body mass index, *ASA PS* American Society of Anesthesiologists Physical Status, *PACU* postanesthetic care unit

[a]Student's *t* test

[b]Fisher's exact test

[c]Chi-squared test

Table 2 Incidence of PONV, nausea, and vomiting and the use of rescue metoclopramide within 24 h of surgery

	Group G ($n=45$)	Group GE ($n=45$)	p value	RR (95% CI)
PONV	27 (60.0)	20 (44.4)	0.14[b]	0.53 (0.23–1.23)
Nausea	26 (57.8)	19 (42.2)	0.14[b]	0.53 (0.23–1.23)
Vomiting	4 (8.9)	4 (8.9)	1.00[a]	1.00 (0.23–4.27)
Use of rescue metoclopramide	18 (40.0)	11 (24.4)	0.11[b]	0.49 (0.20–1.20)

Values are expressed as the number (%)

PONV postoperative nausea and vomiting, *G* general anesthesia, *GE* general anesthesia combined with epidural anesthesia, *RR* relative risk, *CI* confidence interval, *NA* not available

[a]Fisher's exact test

[b]Chi-squared test

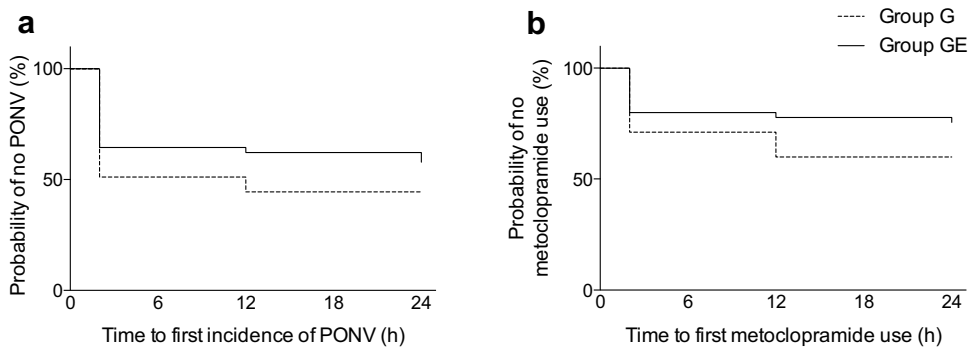

Fig. 1 Time to first incidence of PONV (**a**) and first use of rescue metoclopramide (**b**). *PONV* postoperative nausea and vomiting, *G* general anesthesia, *GE* general anesthesia combined with epidural anesthesia

analgesic agents (i.e., i.v. fentanyl, indomethacin suppository, oral mefenamic acid, oral acetaminophen, intramuscular pentazocine, and i.v. flurbiprofen) were used to treat postoperative pain, we compared the total amount of each agent administered between the study groups (Table 3). The total amount of fentanyl administered in the PACU was significantly lower in group GE than in group G ($p < 0.001$). However, no significant intergroup

Table 3 Amount of rescue analgesics required after surgery

	Group G ($n=45$)	Group GE ($n=45$)	p value
Fentanyl in the PACU (μg)	25 (0–350)	0 (0–50)	<0.001
Indomethacin (mg)	25 (0–75)	25 (0–75)	0.67
Mefenamic acid (mg)	0 (0–500)	0 (0–500)	0.61
Acetaminophen (mg)	0 (0–800)	0 (0–800)	0.31
Pentazocine (mg)	0 (0–30)	0 (0–30)	0.56
Flurbiprofen (mg)	0 (0–0)	0 (0–50)	0.32

Values are expressed as the median (range)

The data were compared using the Mann–Whitney *U* test

G general anesthesia, *GE* general anesthesia combined with epidural anesthesia, *PACU* postanesthetic care unit

differences were observed in the total amounts of other rescue analgesics administered in the ward.

One of the 90 patients in group GE was excluded from the analysis because of failure to complete the questionnaire, leaving survey rating data for 89 patients available for analysis. Patients in group GE were significantly more satisfied with their degree of postoperative nausea ($p=0.001$) and were more likely to choose the same anesthetic method if they required surgery in the future ($p=0.002$). No difference in patient satisfaction with pain management was found between the groups (Table 4). There were no episodes of urinary retention, paresthesia, or postoperative hypotension requiring treatment (with fluids or medication) in either groups. Ambulation on the morning of the first postoperative day was delayed until the afternoon in three (6.7%) patients in group G and five (11.6%) patients in group GE; the difference was not statistically significant, and none of the delays were related to neurologic complications.

Discussion

Recently, several analgesic techniques, including transverse abdominis plane block and wound infiltration with local anesthetic agents, have been used to manage postoperative analgesia in patients undergoing laparoscopic procedures. Although these techniques provide acceptable postoperative analgesia [14], they do not seem to be effective for reducing PONV [15–18]. Given that no single intervention alone can prevent PONV, we sought to reduce the baseline risk of PONV in women undergoing gynecological laparoscopic surgery using approaches other than total intravenous anesthesia, which is already known to reduce PONV [19]. In the present study, we found that 60% of patients who received general anesthesia alone developed PONV within 24 h after surgery, despite administration of dexamethasone, which is one of the most widely used antiemetics for PONV prophylaxis. Although intraoperative opioid administration has not been considered as a risk factor for PONV [2], reducing the opioid dosage should be considered as one of the PONV prophylaxis strategies, since several studies have shown that opioid-free anesthesia reduces PONV in some surgical procedures [8–10]. However, minimizing intraoperative opioid use by concomitant use of general anesthesia and epidural anesthesia failed to reduce the incidence of 24-h PONV in this patient population. This anesthetic approach also did not significantly reduce the use of rescue metoclopramide 24 h after surgery. The Kaplan–Meier analysis showed that most PONV episodes occurred within 2 h after surgery, even in the patients in group GE, suggesting that sevoflurane, which has been shown to be associated with PONV in the early postoperative period [20], had a greater influence on PONV in comparison with the intraoperative opioid dosage. A meta-analysis of 9044 surgical patients showed that postoperative epidural analgesia had beneficial effects on gastrointestinal symptoms such as ileus and PONV in comparison with systemic opioid analgesia [21]. However, we found no beneficial effects of epidural anesthesia on PONV in the present study. The patients in group G did not receive postoperative systemic opioids, which might have affected the results of the study. In addition, a recent study showed that even a single dose of fentanyl administered during anesthesia induction can cause PONV [22], which might also have affected the results of this study.

In our study, despite using high-dose intraoperative fentanyl, more than half of the patients who received general anesthesia alone required rescue fentanyl in the PACU, which is comparable to the findings of previous studies showing that pain intensity levels are high in the immediate postoperative period after some laparoscopic procedures [23, 24]. Our present results indicate that adequate intraoperative and postoperative pain management is essential in patients undergoing laparoscopic gynecological surgery. As expected, the concomitant use of epidural anesthesia with general anesthesia reduced rescue fentanyl requirements in the PACU. However, this anesthetic technique did not reduce the use of other rescue analgesics in the main ward. Furthermore, patient satisfaction with postoperative pain

Table 4 Patients' satisfaction with their levels of nausea and pain after surgery and their preference for anesthesia in any future surgeries

	Group G ($n=45$)		Group GE ($n=44$)		p value
	Score	n	Score	n	
Question 1	2 (1–5)		1 (1–4)		0.001
Satisfaction with nausea					
	1	19	1	31	
	2	11	2	10	
	3	6	3	1	
	4	5	4	2	
	5	4	5	0	
Question 2	2 (1–4)		2 (1–5)		0.05
Satisfaction with pain					
	1	11	1	18	
	2	19	2	17	
	3	7	3	7	
	4	8	4	1	
	5	0	5	1	
Question 3	2 (1–5)		1 (1–3)		0.002
Preference on anesthesia					
	1	14	1	27	
	2	17	2	12	
	3	8	3	5	
	4	4	4	0	
	5	2	5	0	

A total of 89 survey results were analyzed. One patient in group GE did not answer the questionnaire. The values are expressed as the median (range)

The data were compared using the Mann–Whitney *U* test

Satisfaction with levels of nausea and pain: *1* very satisfied, *2* satisfied, *3* neutral, *4* unsatisfied, *5* very unsatisfied

Preference for anesthesia: *1* very likely, *2* likely, *3* neutral, *4* unlikely (if there is another technique), *5* very unlikely (if there is another technique)

G general anesthesia, *GE* general anesthesia combined with epidural anesthesia

management was not different between the study groups. These data suggest that short-term opioid-free epidural analgesia is not superior to multimodal analgesia after laparoscopic gynecological surgery.

Hubner et al. [25] reported that epidural anesthesia caused hemodynamic instability and impeded recovery after laparoscopic colorectal surgery. In the present study, epidural anesthesia did not increase the amounts of ephedrine and fluids administered intraoperatively or the incidence of postoperative hypotension requiring treatment. This discrepancy in findings could be attributed to the different patient populations in the two studies, in that the patients in our study were younger and had lower ASA PS scores than those in the study by Hubner et al. Moreover, we did not find an association between epidural anesthesia and urinary retention, which is in contrast with the results of another study [26]. This is probably because epidural infusion was terminated at least several hours before the removal of the urinary catheter and no opioids were added to ropivacaine in our study [27].

The choice of anesthesia should be based on the risk–benefit ratio and cost-effectiveness. In this study, more patients in group GE than in group G reported being likely to choose the same method of anesthesia if they required surgery in the future. However, epidural anesthesia carries a potential risk of neurological complications [28–30]. Although we did not observe any such complications in our study, the number of patients included was insufficient to determine the frequency of significant adverse events. Therefore, studies with larger sample sizes are needed in the future to examine this issue.

Our study has several limitations. First, it was not performed in a double-blind manner because of the nature of the study intervention. Although the investigator who performed the data analyses was blinded to group allocation and was not involved in the postoperative assessments, the lack of full blinding might have affected the present findings. Second, several analgesic agents were used to treat postoperative pain; therefore, the effects of the anesthesia method on postoperative analgesia were not evaluated quantitatively

and the differences in the doses of analgesics administered between the two groups might have been underestimated.

In conclusion, minimizing intraoperative opioid use by combining general and epidural anesthesia reduced neither the 24-h incidence of PONV nor the use of rescue metoclopramide for treating established PONV in patients undergoing laparoscopic gynecological surgery. It would be difficult to justify the use of this approach in patients undergoing minimally invasive surgical procedures.

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