Original articles



The effect of anesthetic technique on early postoperative gastric emptying: comparison of propofol-remifentanil and opioid-free sevoflurane anesthesia

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Abstract

Purpose. A postoperative decrease in the gastric emptying (GE) rate may delay the early start of oral feeding and alter the bioavailability of orally administered drugs. The aim of this study was to compare the effect on early gastric emptying between two anesthetic techniques.

Methods. Fifty patients (age, 19–69 years) undergoing day-case laparascopic cholecystectomy were randomly assigned to received either total intravenous anesthesia with propofol/remifentanil/rocuronium (TIVA; n = 25) or inhalational opioid-free anesthesia with sevoflurane/rocuronium (mask induction; GAS; n = 25). Postoperative gastric emptying was evaluated by the acetaminophen method. After arrival in the recovery unit, acetaminophen (paracetamol) 1.5 g was given through a nasogastric tube, and blood samples were drawn during a 2-h period. The area under the serum-acetaminophen concentration curve from 0–60 min (AUC₆₀), the maximal concentration (C_{max}), and the time to reach C-max (T_{max}) were calculated.

Results. Twelve patients were excluded due to surgical complications (e.g., conversion to open surgery) and difficulty in drawing blood samples (TIVA, n = 7; GAS, n = 5). Gastric emptying parameters were (mean \pm SD): TIVA, AUC60, 2458 \pm 2775 min·µmol·l⁻¹; Cmax, 71 \pm 61 µmol·l⁻¹; and Tmax, 81 \pm 37 min; and GAS, AUC60, 2059 \pm 2633 min·µmol·l⁻¹; Cmax, 53 \pm 53 µmol·l⁻¹; and Tmax, 83 \pm 41 min. There were no significant differences between groups.

Conclusion. There was no major difference in early postoperative gastric emptying between inhalation anesthesia with sevoflurane versus total intravenous anesthesia with propofolremifentanil. Both groups showed a pattern of delayed gastric emptying, and the variability in gastric emptying was high. Perioperative factors other than anesthetic technique may have more influence on gastric emptying.

Key words Gastrointestinal motility · Gastric emptying · Anesthesia, inhalation · Anesthesia, intravenous · Analgesics, opioid · Cholecystectomy, laparoscopic

Introduction

Gastric emptying is an essential part of gastrointestinal motility, and a postoperative delay may postpone the early start of oral feeding and alter the bioavailability of orally given drugs [1]. Today a majority of our patients undergo surgery on an ambulatory basis and an important part of the care is to have them tolerate oral nutrition and per-oral analgesics as soon as possible. A delay in gastric emptying may therefore postpone a patient's discharge.

Activation of inhibitory neural pathways by the surgical trauma, a local inflammatory response in the gastrointestinal tract, and the drugs used perioperatively contribute to the impairment of gastric motility [2], and, of the drugs used, opioids are thought to constitute the most important factor.

The extent to which anesthetic technique contributes to the early postoperative inhibition of gastric motility is uncertain. With an inhalation technique without opioids, the effect of inhalation agents on gastric motility may cease quickly after discontinuation of the agent [3]. An intravenous technique with an ultra-shortacting opioid, to minimize the negative opioid effect on motility, combined with propofol, which has antiemetic properties, and to some degree, antagonizes the opioid effect on gastric motility [4], may favor motility. Both methods are, theoretically, optimal for gastric motility. However, when these anesthetic techniques are used in major surgery there may be a need for opioid analgesics in the early postoperative period, as the residual analgesic properties of the anesthetics cease quickly. If one of the techniques proves to have a faster gastric emptying rate, this may have an impact on the choice of anesthesia to optimize gastric motility.

The aim of this study was to compare the effect on early gastric emptying between two anesthetic methods, an inhalation opioid-free sevoflurane-based anesthesia

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and an intravenous propofol-remifentanil based anesthesia.

Patients, materials, and methods

Fifty patients (American Society of Anesthesiologists [ASA] physical status I and II) undergoing day-case laparoscopic cholecystectomy at Örebro University Hospital, Sweden, were included in this study. The study protocol was approved by the Ethics Committee of the Orebro County Council and by the Swedish Medical Product Agency. The patients entered the study after giving verbal and written consent. Patients were randomly allocated (by the use of sealed envelopes) to receive either total intravenous anesthesia (TIVA group; n = 25) or total inhalation anesthesia (GAS group; n = 25). An independent nurse prepared all the sealed envelopes from of a computer-generated table before the study started. Investigators (J.W., M.W., S.E.T.) enrolled patients to the study. The envelopes were opened by the investigators just before the induction of anesthesia. There was no blinding in the study.

Patients were excluded from the study if the procedure was converted to open cholecystectomy, or if the duration of surgery exceeded 150 min.

The gastric emptying study was started immediately after the patient's arrival at the recovery unit. During the first 24h after surgery, the incidence of postoperative nausea and vomiting (PONV) and pain, and the need for opioid analgesics were evaluated by means of observations in the recovery unit, a telephone interview, and a questionnaire.

The primary endpoints in the study were the gastric emptying parameters, and we tested the hypothesis that there would be a difference in gastric emptying between the study groups.

For the secondary outcome variables (PONV, pain, opioid need) we were aware that the number of patients might be too small to detect differences.

The patients fasted for 6h but were allowed to drink clear fluids up to 2h before premedication. All patients received premedication with midazolam 1-2mg IV at the day-care unit, 20-30 min before the induction of anesthesia. In the operating room, patients underwent routine monitoring, including continuous processed electroencephalography (Bispectral index |BIS|monitor; Aspect Medical Systems, Newton, MA, USA). Before induction, all patients received ketorolac 30 mg IV. In the TIVA group, anesthesia was induced with an infusion of remifentanil 0.2 µg·kg⁻¹·min⁻¹, followed, after 2min, by a target-controlled infusion (TCI) of propofol at $4\mu g \cdot ml^{-1}$ (induction time, 60s). In the GAS group, anesthesia was induced with 8% sevoflurane via a facial mask. After an adequate level of anesthesia was attained, muscular relaxation was obtained in both groups with rocuronium 0.6 mg·kg⁻¹ IV, and the trachea was intubated after 90s. In the TIVA group, anesthesia was maintained with remifertanil 0.2µg·kg⁻¹·min⁻¹ and TCI propofol, adjusted (2-4µg·ml-1) to maintain a BIS index below 50. In the GAS group, anesthesia was maintained with sevoflurane, with concentrations adjusted to maintain a BIS index below 50. No prophylactic antiemetics were given. A nasogastric tube was placed in all patients during anesthesia. At the end of surgery, 20 ml of 0.25% levobupivacaine was infiltrated at the insertion sites of the laparoscopic instruments, muscular relaxation was reversed with neostigmine 2.5 mg/glycopyrrolate 0.5 mg, and anesthetic agent(s) were terminated. The patients were extubated in the operating room after return of consciousness and spontaneous breathing and transferred to the adjacent day-care unit for recovery. Except for the continuous infusion of remifentanil in the TIVA group, no opioids were given during anesthesia.

Acetaminophen absorption was used as an indirect measure of gastric emptying [5]. Acetaminophen is not absorbed from the stomach, but is rapidly absorbed from the small intestine. Consequently, the rate of gastric emptying determines the rate of absorption of acetaminophen administered into the stomach. Immediately after patients' arrival at the day-care unit, acetaminophen 1.5g, dissolved in 200ml of water (at room temperature), was given through the nasogastric tube. Prior to administration, correct placement of the tube was verified by auscultation over the stomach area during the injection of 20ml of air into the tube. The tube was removed after acetaminophen was given. Blood samples were taken from an intravenous catheter prior to the administration of acetaminophen and then 5, 10, and 15 min after the administration, and then at 15-min intervals during a period of 120min. Serum acetaminophen was determined by an immunologic method, including fluorescence polarization (TDx acetaminophen; Abbott Laboratories, Chicago, IL, USA). Acetaminophen concentration curves were produced, and the maximal acetaminophen concentration (C_{max}) , the time taken to reach the maximal concentration (T_{max}) , and the area under the serum-acetaminophen concentration time curves from 0 to $60 \min (AUC_{60})$ and 0 to 120 min (AUC₁₂₀) were calculated. T_{max} was assumed to be 120 min if no acetaminophen was detected in any sample. The acetaminophen method is a wellaccepted method for studying the liquid phase of gastric emptying, and the AUC_{60} correlates well with measures of gastric emptying performed using isotope techniques [5].

The patients stayed in the day-care unit for at least 4h. During this period, nausea, vomiting, and pain were

evaluated every hour. Nausea and pain were evaluated with a visual analogue scale (VAS), and occurrences of vomiting were recorded. Droperidol 0.5–1 mg IV was given on request as the first rescue antiemetic according to the routines of the department. If not sufficient, ondansetron 2–4 mg IV was given as the second drug. If patients scored more than 3 on the VAS for pain, ketobemidone 1–2 mg IV was given. Ketobemidone is an opioid analgesic with properties similar to those of morphine and is widely used in the Scandinavian countries.

After discharge from the day-care unit, the patients themselves completed a questionnaire about PONV and pain during the time period 4-24h postoperatively. The patients scored the maximal pain and maximal nausea on a VAS and were questioned as to whether they had vomited or not. A nurse or doctor also performed a telephone interview on the first postoperative day, during which patients were questioned about events of pain, nausea, or vomiting after discharge. Combining the observations from the recovery unit, the questionnaire, and the telephone interview, we acquired variables regarding the incidence of PONV during 0-2h and 2–24 h, the need for antiemetics in the day-care unit, the maximal VAS score for pain during the periods 0-2h and 2-24h, the time to first dose of opioid analgesics, and the total dose of opioids given. These variables were regarded as secondary outcome variables in the study.

Sample size was calculated based on the AUC₆₀ as the primary outcome variable. A difference of at least one-third of AUC₆₀ under normal conditions was considered clinically significant. Based on previous studies [6], we estimated the minimal difference to be 2000 min·µmol·l⁻¹ and the within-group SD for the AUC₆₀ to be 2000 min·µmol·l⁻¹. For a power of 0.8

and $\alpha = 0.05$, a sample size of 17 patients in each group was calculated to be appropriate. From previous studies with the acetaminophen method, we had the experience that, in some patients, it might be difficult to draw venous blood samples due to a constricted venous system. For this reason, we increased the study population to 25 patients in each group.

To be able to compare our gastric-emptying results with a normal gastric-emptying profile (in our context without any influence from anesthesia, surgery, pain, drugs, etc) we used a pooled dataset of control gastric-emptying measurements from three previous studies by our group. In the first study [6] the controls were taken 4-5 weeks after an open cholecystectomy (n = 17; ASA, I–II; mean (\pm SD) age, 49 \pm 15 years; male, n = 4; female, n = 13); in the second study (unpublished data), 4 weeks after abdominal surgery (n = 9; ASA, I–II; mean age, 69 ± 10 years; male, n = 7; female, n = 2); and in the third study, the controls were young healthy male volunteers in an experimental setting [7] (n = 10;ASA, I; mean age, 24 ± 3.4 years). In all control measurements, 1.5g acetaminophen dissolved in 200 ml of water was given orally after a period of fasting and blood samples were taken every 15 min during 2h. The handling and laboratory analysis of the samples were the same as in the current study, as described above. The mean serum-acetaminophen concentration curve of the pooled data is presented in Fig. 1, and the gastric emptying parameters were (mean \pm SD): AUC₆₀, $5988 \pm 1713 \min \mu \text{mol·l}^{-1}$; C_{max}, $145 \pm \mu \text{mol·l}^{-1}$; and T_{max}, $29 \pm 15 \,\mathrm{min.}$

The primary outcome variables AUC_{60} , AUC_{120} , C_{max} , and T_{max} , are presented as means with SDs. The secondary outcome variables are presented as events, numbers, or medians with ranges. Unpaired Student's *t*-test, Mann-Whitney *U*-test, or Fisher's exact test was used

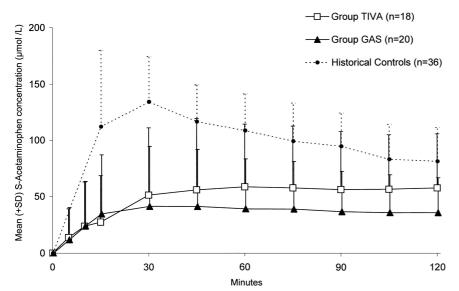


Fig. 1. Mean (+SD) serum (S)acetaminophen concentrations during the gastric emptying study after propofolremifentanil total intravenous anesthesia (TIVA) or opioid-free sevoflurane (GAS) anesthesia. As a reference for normal gastric emptying, a group of historical controls, pooled from control groups in three previous studies (see the Methods section for description), is included in the graph

	TIVA group $(n = 24)$	GAS group $(n = 21)$	P value ^a
Age (years)	45 (29–64)	46 (19-69)	NS
Height (cm)	168 (152–189)	169 (158–187)	NS
Weight (kg)	80 (56–112)	75 (56–100)	NS
Females	20	16	NS
Males	4	5	NS
Smokers	4	4	NS
ASA Class I	19	17	NS
ASA Class II	5	4	
Duration of surgery (min)	74 (25–148)	70 (65–108)	NS
Duration from end of surgery to tracheal extubation (min)	8 (2–17)	9 (2–22)	NS
Duration from end of surgery to arrival at recovery unit (min)	19 (10–30)	22 (8–45)	NS
Duration from end of surgery to start of GE study (min)	24 (13–35)	26 (17–45)	NS

 Table 1. Patient characteristics and time variables before the start of the gastric emptying study

Values are given as means with ranges or numbers

TIVA, total intravenous anesthesia with remifentanil and propofol; GAS, total inhalation

anesthesia with sevoflurane; GE, gastric emptying

^a Unpaired Student's *t*-test or Fisher's exact test

Table 2. Mean and SI	D of AUC_{60} , AUC_{120} ,	C_{max} , and T_{max} in	the two study groups
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Variable	TIVA group $(n = 18)$	GAS group $(n = 20)$	95% CI for the difference between the means	P value ^a
AUC_{60} (min·µmol ⁻¹ ·l ⁻¹)	2458 ± 2775	2059 ± 2633	-1390 to 2188	NS ($P = 0.65$)
AUC_{120} (min·µmol ⁻¹ ·l ⁻¹)	5889 ± 5750	4288 ± 4820	-1877 to 5079	NS $(P = 0.36)$
$C_{max}(\mu mol \cdot l^{-1})$	71 ± 61	53 ± 55	-20 to 56	NS $(P = 0.35)$
$T_{max}(min)$	81 ± 37	83 ± 41	-28 to 24	NS $(P = 0.85)$

TIVA, total intravenous anesthesia with remifentanil and propofol; GAS, total inhalation anesthesia with sevoflurane; AUC_{60} , AUC_{120} , area under the serum-acetaminophen concentration curve at 0–60 min and 0–120 min; C_{max} , maximum acetaminophen concentration; T_{max} , time taken to reach the maximum acetaminophen concentration; CI, confidence interval; NS, not significant

^a Unpaired Student's *t*-test

for statistical analysis, and P < 0.05 was considered statistically significant.

 Table 3. Number of patients without detectable serum acetaminophen (no gastric emptying at all) at different time periods

	TIVA group $(n = 18)$	GAS group $(n = 20)$	P value ^a
0–60 Min	3	1	NS
0–120 Min	1	0	NS

Results

Fifty patients were included in the study from April 2002 to January 2003. Five patients (TIVA, n = 4; GAS, n = 1) were excluded due to conversion to open cholecystectomy or prolonged duration of surgery (>150 min) due to choledochal stones. In 7 patients (TIVA, n = 3; GAS, n = 4) there were difficulties in drawing blood samples for the acetaminophen concentration analysis. Hence, a total of 12 patients (TIVA, n = 7; GAS, n = 5) were excluded from the analysis of the primary outcome variable.

Patient characteristics are presented in Table 1. Surgery and anesthesia were uneventful in all patients. There were no differences between the groups in duration of surgery or duration from end of surgery to start of the gastric emptying studies. TIVA, total intravenous anesthesia with remifentanil and propofol; GAS, total inhalation anesthesia with sevoflurane; NS, not significant ^aFisher's exact test

Acetaminophen concentration curves are presented in Fig. 1. There were no differences between the groups in the primary outcome variables, AUC_{60} , AUC_{120} , C_{max} , or T_{max} (Table 2). Both groups differed significantly (P < 0.01) from the pooled historical control group. Of the 38 patients eligible for the primary outcome analysis, only 1 patient had no detectable acetaminophen in any of the blood samples (i.e., no gastric emptying at all); see Table 3.

Variable	TIVA group $(n = 21)$	GAS group $(n = 24)$	P value ^a
Postoperative 0–2h			
Nausea	10 (48%)	15 (62%)	NS
Vomiting	2 (10%)	4 (17%)	NS
Nausea or vomiting	10 (48%)	16 (67%)	NS
Postoperative 2–24 h			
Nausea	11 (52%)	16 (67%)	NS
Vomiting	5 (24%)	8 (33%)	NS
Nausea or vomiting	12 (57%)	16 (67%)	NS
Postoperative 0–24 h			
Nausea	15 (71%)	20 (83%)	NS
Vomiting	6 (29%)	8 (33%)	NS
Nausea or vomiting	16 (76%)	20 (83%)	NS

Table 4. Numbers (%) of patients with events of postoperative nausea and/or vomiting (PONV) during the study

TIVA, total intravenous anesthesia with remifentanil and propofol; GAS, total inhalation anesthesia with sevoflurane; NS, not significant

Event of nausea 0–2h, VAS for nausea >10mm at day-care unit; event of nausea 2–24h, VAS for nausea >10mm at day-care unit or VAS for nausea >10mm on questionnarie, or nausea reported at telephone interview; VAS, 100-mm visual analogue scale

^aFisher's exact test

Table 5. Pain variables

Variable	TIVA group	GAS group	P value ^a
	<i>n</i> = 21	<i>n</i> = 24	
Median (range) for the highest VAS score for pain 0–2h	5 (0-9)	4 (0-9)	NS
Median (range) for the highest VAS score for pain 2–24h	4 (0-10)	4 (0-7)	NS
Number of patients with need for opioid analgesics in recovery unit	17 (81%)	20 (83%)	NS
	<i>n</i> = 17	n = 20	
Median (range) total dose of ketobemidone IV (mg) in patients who received opioid analgesics	5.9 (1.5–11)	5.0 (2.0–11)	NS
Median (range) time from arrival at recovery unit to first dose of ketobemidone (min) in patients who received opioid analgesics	17 (0-45)	44 (0–155)	< 0.01

TIVA, total intravenous anesthesia with remifentanil and propofol; GAS, total inhalation anesthesia with sevoflurane; NS, not significant; VAS, 100-mm visual analogue scale

^a Mann-Whitney U-test or Fisher's exact test

Secondary outcome variables were obtained in 45 patients (TIVA, n = 21; GAS, n = 24). The questionnaire was completed by 20 patients (95%) in the TIVA group and 23 patients (96%) in the GAS group. The telephone interview was performed in 20 patients (95%) in the TIVA group and 22 patients (92%) in the GAS group. For the period 2–24h postoperatively, secondary outcome variables could be obtained in all patients.

There were no statistically significant differences between the groups in the incidence of nausea, vomiting, or PONV (Table 4). Twelve (57%) patients in the TIVA group and 10 (42%) patients in the GAS group were given rescue antiemetics in the recovery unit.

There were no differences between the groups in maximal VAS scores for pain, the need for opioid analgesics, or the dose of opioid analgesics. The time to the first administration of opioids in the recovery unit was significantly longer in the GAS group (Table 5).

Discussion

This study demonstrates that patients anesthetized with an inhalational, opioid-free regimen with sevoflurane had a gastric emptying pattern in the early postoperative period (0-2h) similar to that in patients anesthetized with an intravenous propofol-remifentanil regimen. When our results were compared with the gastric emptying pattern seen in a normal state (no anesthesia and no surgery), gastric emptying could be considered to be delayed in both groups. Our study was powered to detect major differences in gastric emptying rate, and the results indicate that there might be a small difference, with faster gastric emptying in the total intravenous anesthesia group. However, gastric emptying was greatly delayed in both groups, and we do not consider a potential difference of this small magnitude as clinically relevant.

There was great variability in the gastric emptying rate within the groups. We tested the hypothesis of a correlation between opioid administration in the early postoperative period and gastric emptying rate, but we found no relation (data not shown). There was both fast and slow emptying among patients who received opioid analgesics during the gastric emptying study, as well as among those who did not receive any opioid analgesics or those who received opioid analgesics after the gastric emptying study was completed. The use of opioid analgesics and antiemetics in the recovery period is part of the overall perioperative care of the patients and is partly a consequence of the anesthetic technique. These factors cannot be eliminated and should be considered as part of the anesthetic technique.

It is always doubtful to include historical data as a control. However, we thought it would be valuable to relate the gastric emptying profile seen in the groups in the present study to a normal gastric emptying profile, which, in our context, means under no influence of anesthesia, surgery, drugs, pain etc. To create a reference, we pooled data from control situations in three previous studies performed under different conditions. The gastric emptying profiles for these data, both the individual control groups and the pooled group, are similar to those in other control situations published in the literature [8–10]. We consider our control dataset as an acceptable estimate of a normal gastric emptying profile. It would have been ideal to have control values for each patient included in the study, but, unfortunately, that was not the study design.

We were aware that the number of patients might be too small to detect any differences in postoperative nausea and vomiting (PONV) [11], and we could not detect any statistically significant differences in PONV between the groups. PONV was not a primary endpoint in this study, but we considered it valuable to have the PONV recordings. There was a tendency in our study toward a higher incidence of PONV in the GAS group, and it has been reported that volatile agents may be a main cause of vomiting in the early postoperative period [12]. To draw any conclusions about differences in PONV between the anesthetic techniques, a larger number of patients must be studied.

The incidence of PONV was high in both groups. The majority of patients were non-smoking women, and opioids were given as analgesics in the recovery unit. If Apfel's simplified risk score [13] were to be applied, the predicted incidence of PONV would be high in patients with these characteristics. As there are no data on how antiemetics affect gastric emptying, no prophylactic antiemetics were given.

There is probably no direct relation between gastric emptying and PONV. We have previously shown that the perioperative gastric emptying rate is not a predictor for PONV [14], and gastric decompression during anesthesia does not reduce the incidence of PONV [15].

There was a shorter time to the first dose of postoperative opioid analgesics in the group receiving the intravenous anesthesia. This may be explained either by a residual effect of the inhalation agent [16] or by hyperalgesia caused by remifertanil [17].

Previous studies comparing the effects on gastrointestinal motility exerted by different general anesthetic techniques in the clinical situation are limited, and these have not shown any differences between different techniques [9,18,19]. The results from our study are in accordance with these study results, as we found no major differences between the groups. Nothing can be concluded as to what extent the anesthetics used are involved in the postoperative impairment of gastrointestinal motility. Other factors, such as the surgical trauma or individual sensitivity to the drugs used may be more important.

There are several experimental studies addressing the effects of anesthetic drugs on gastrointestinal motility. The inhibitory effect of opioids on gastrointestinal motility has been studied extensively. This effect is mainly mediated via opioid receptors, but the mechanism and understanding are complex and still uncertain [20]. Opioids inhibit motility even at low doses [21], and the mechanism is both peripherially and centrally mediated [22]. Propofol at low doses does not influence gastric motility [23], but there is evidence that propofol may inhibit motility at higher doses. In a laboratory setting, propofol inhibited spontaneous contractions in human gastric tissue [24]. There are only a few studies on volatile agents and gastrointestinal motility. Volatile anesthetics have inhibitory effects on gastric motility, but the effect may cease quickly after termination of the agents [3, 25].

The anesthetic techniques used in this study, one opioid-free and one with an ultra-short-acting opioid, would, theoretically, be ideal for optimizing gastric emptying. However, the majority of patients had delayed gastric emptying with both of these methods. This indicates that it may be difficult to further improve early gastric emptying by further altering the methods of general anesthesia. We cannot exclude the possibility that all general anesthetic methods have inhibitory effects on early postoperative gastric emptying. Other perioperative factors may also have main impacts on early gastric emptying, and it is difficult to distinguish between all the factors involved. However, intraoperative and postoperative intravenous fluid restriction promotes the return of gastrointestinal motility and reduces complications after abdominal surgery [26]. Minimizing the surgical trauma during the laparoscopic procedure reduces pain and nausea [27].

The weakness in our study is that the variability of gastric emptying was higher than expected, which resulted in loss of power. However, we believe that our study indicates that, even after optimizing the anesthetic regimen, gastric emptying is delayed for the majority of patients. In both groups there were several patients with fast gastric emptying and there may also have been a small difference between the groups that was not detected in our study. The high variability may have been due to factors other than the anesthetics used, and must be addressed in future studies.

In summary, there were no major differences in early postoperative gastric emptying between opioid-free sevoflurane anesthesia and intravenous propofolremifentanil anesthesia. The variability was high in both groups, and perioperative factors other than the anesthetics used may have greater influence on early postoperative gastric emptying.

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