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ORIGINAL ARTICLE

Effect of scheduled intravenous acetaminophen on postoperative nausea and vomiting in patients undergoing laparoscopic gynecologic surgery

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Abstract

Purpose The aim of this study was to assess the effect of scheduled intravenous acetaminophen (SIVA) on the incidence of postoperative nausea and vomiting (PONV) in patients undergoing laparoscopic gynecologic surgery (LGS).

Methods This retrospective observational study identified consecutive patients who underwent LGS at our institution from January to November of 2017 and were managed with either our hospital's old protocol (Group H) or a new protocol using SIVA (Group S). Primary outcomes included the incidences of PONV and the amount of additional antiemetic required in the postoperative period. The secondary outcomes included the pain score on postoperative day 1, the requirement for additional analgesic medications, and the length of hospitalization (LOH).

Results Patients in Group S had significantly lower incidences of PONV from postoperative days 0 to 1 and required significantly less antiemetics or tramadol than those in Group H ($P=0.0085$). Patients at a low risk for PONV in Group S had significantly lower incidences of PONV than those in Group H ($P=0.0129$). Further, the amount of additional tramadol required was lower in Group S than in Group H ($P=0.0021$).

Conclusion Introduction of SIVA into the postoperative pain management protocol of LGS may reduce the incidence of PONV and the amount of adjunctive antiemetic medication required from postoperative days 0 to 1. In patients undergoing LGS, PONV prophylaxis using antiemetics should be prescribed depending on PONV risk profile; however, SIVA prophylaxis can be used in all patients regardless of PONV risk profile.

Keywords Scheduled intravenous acetaminophen · Acetaminophen · Laparoscopic gynecologic surgery · Opioid sparing · Postoperative nausea and vomiting

Introduction

Evidence-based guidelines for the perioperative care of patients undergoing various surgical procedures have been published by the Enhanced Recovery After Surgery (ERAS) Society [1, 2]. ERAS guidelines for gynecologic/oncologic surgeries (ERASG) have recently been updated and recommend scarce opioid administration in patients undergoing gynecologic or oncologic surgical procedures to facilitate an earlier return of bowel function and a shorter length of hospitalization (LOH). Moreover, according to these guidelines, multimodal non-opioid analgesia use in these patients decreases postoperative nausea and vomiting (PONV) and allows for a more rapid recovery [3]. One of the simplest methods to limit opioid intake in the postoperative period is to schedule narcotic alternatives including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and gabapentin rather than administering them on an as-needed basis [4]. The scheduled use of selective or nonselective NSAIDs, cyclooxygenase (COX) 2 inhibitors, and acetaminophen (orally or intravenously [IV]) has been shown to improve postoperative analgesia and reduce the consumption of systemic opioids and their dose-dependent adverse effects

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[5, 6]. A meta-analysis of 30 randomized controlled trials (RCTs), which included 2364 patients, showed that administering acetaminophen IV either before surgery or before arrival at the post-anesthesia care unit reduced the risk of nausea and pain, both of which are known to delay surgical recovery [6].

As Japanese insurance processes restrict the use of perioperative antiemetic agents, the rate of PONV remains high in Japan, especially after gynecologic surgery. We hypothesize that opioid sparing using SIVA may be an effective strategy to decrease the rate of PONV for patients undergoing laparoscopic gynecologic surgery (LGS) in Japan. In 2011, the accepted clinical dosage of IV acetaminophen in Japan increased from a maximum of 1500 to 4000 mg per day to allow for a more optimal analgesic effect. To date, however, there have been few clinical studies evaluating this new maximum dosage of acetaminophen. Moreover, acetaminophen is often prescribed to patients only on an as-needed basis depending on their pain levels, with few studies or recommendations evaluating the use of scheduled IV acetaminophen (SIVA) in postoperative patients.

The aim of this study was to assess the effect of SIVA on the incidence of PONV and the efficacy of analgesia in patients undergoing LGS according to our hospital's management protocols. We included patients specifically undergoing LGS because these procedures allow us to assess the isolated effects of SIVA on PONV without potential confounding factors related to the use of epidural anesthesia or IV opioids.

Methods

The present study was approved by the Institutional Review Board of Saiseikai Yokohamashi Tobu Hospital (Approval no. 2016090), was registered with the Center for Clinical Trials, Japan Medical Association (JMA) Clinical Trials Registry (JMA registration no.: JMA-IIA00326), and was conducted after disclosure of information. The requirement for informed consent was waived because of the retrospective nature of the study. We included patients who had undergone elective LGS for benign diseases of the uterus or ovaries and had been managed postoperatively using either our hospital's old or new pain management protocols.

In our hospital's old LGS pain management protocol, tramadol (a weak opioid) and acetaminophen were used on an as-needed basis (Table 1), and patients were discharged in the morning of postoperative day 4. On June 1, 2017, our hospital initiated a new pain management protocol that used SIVA after LGS (Table 1, Fig 1). The switchover to the new protocol took place during a transition period between June 1, 2017 and June 30, 2017.

For this retrospective study, we reviewed medical records to identify consecutive patients who underwent LGS between January 1, 2017 and May 31, 2017 and were managed using the old pain management protocol. These patients were enrolled in our study and designated as the historical group (Group H). Consecutive patients who underwent LGS between July 1, 2017 and November

Table 1 Management protocol regarding laparoscopic gynecologic surgery

Period	The old protocol (Group H)	The new protocol (Group S)
Preoperative	Major components[a]	
	Intake of oral rehydration solution[b] until 2 h before surgery	
	No laxative medication and premedication	
	Thorough oral cavity care	
Intraoperative	Use of short-acting anesthetics	
	Patient is kept warm[c]	
	Intravenous acetaminophen injected 30 min before the end of surgery. Wound infiltration with local anesthetic is performed	
	Prevention of PONV during operation	
Postoperative	Early ambulation and oral diet (postoperative day 1)	Early ambulation and oral diet (postoperative day 1)
	On the operative day, intravenous infusion of acetaminophen Tramadol is taken as needed repeatedly[d]	Scheduled intravenous acetaminophen and tramadol administered on an as-needed basis[d]

[a]Information sharing/patient education (before and after surgery)

[b]500-ml plastic bottles (OS-1, classified as a type of food in Japan (Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan). We provided 1500 ml of the solution to the patients at 20:00 h on the night before surgery and allowed them to drink at least 500 ml at any time until 2 h before entering the operating room

[c]While the body surface was covered with blankets or towels, the patient was kept warm with a Bair Hugger (3 M, St. Paul, MN) set at 38 °C. The target body temperature was set at a bladder temperature of 36–37 °C. The fluids used were warmed to 35–36 °C with a warming device before transfusion

[d]The maximum total amount of tramadol used (intravenous or/and oral)was up to 300 mg per day

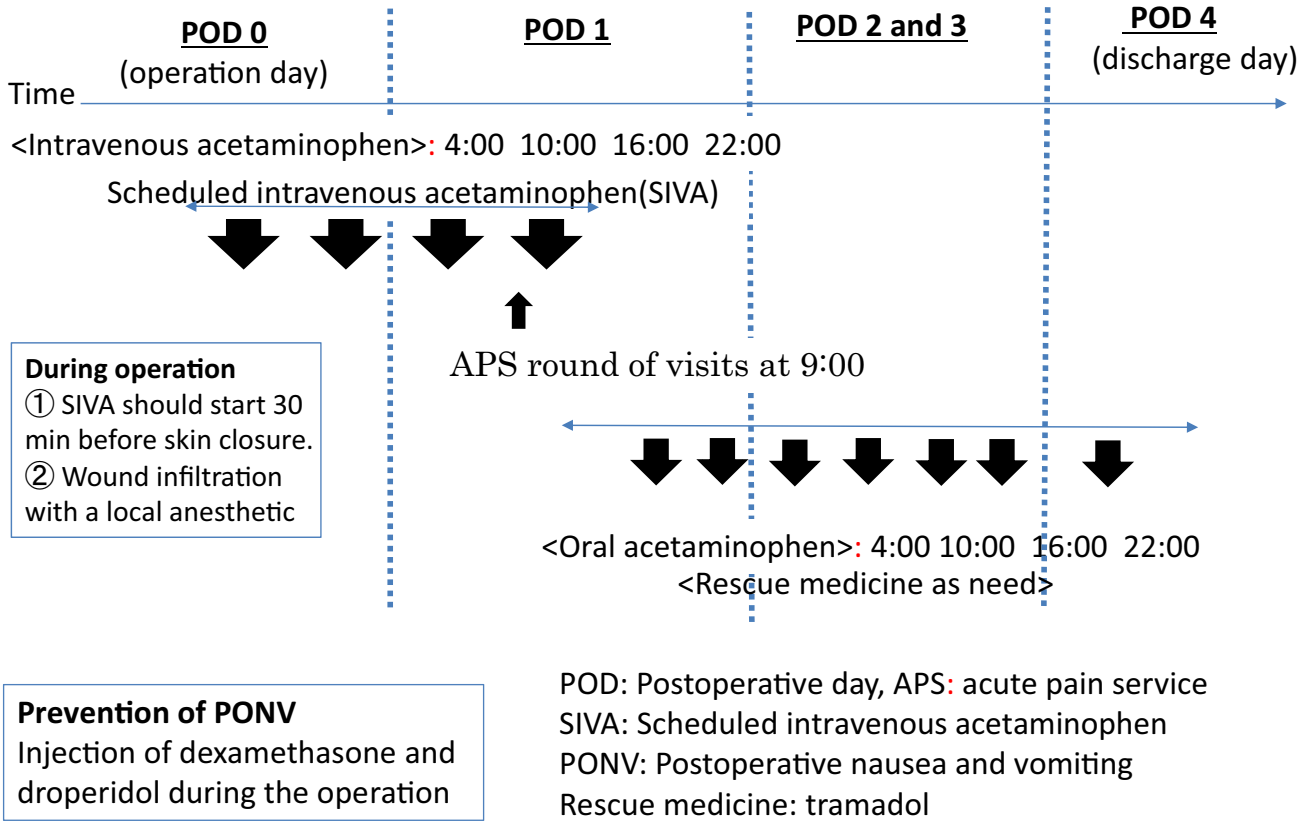

Fig. 1 Pain management protocol for laparoscopic gynecologic surgery. IV acetaminophen was injected 30 min before the end of surgery, and every 6 h for 48 h, with a total of four doses of 1000 mg for patients weighing ≥ 50 kg or 15 mg/kg for patients weighing < 50 kg. Wounds were infiltrated with a local anesthetic (20–40 ml of 0.2% ropivacaine). On postoperative day 1, patients transitioned to oral acetaminophen

30, 2017 and who were managed following the new SIVA protocol were enrolled and designated as the study group (Group S).

The inclusion criteria included patients aged 20 years or older who were categorized as class I or II by the American Society of Anesthesiologists Physical Status (ASA-PS) scale. The exclusion criteria included patients with renal dysfunction (estimated creatinine clearance < 20 ml/min or ongoing hemodialysis), liver dysfunction (AST or ALT > 100 U/l), prescribed NSAIDs on postoperative day 0 or 1, and/or deviation from our hospital's standard LGS management protocols.

This study compared patients treated with two different pain management protocols (with and without SIVA) (Table 1). The primary outcomes were the incidences of PONV during postoperative days 0 to 1 and the patient requirement for an additional antiemetic in the postoperative period. The secondary outcomes included pain score on postoperative day 1, the patient requirement for additional analgesic medications, and length of hospitalization (LOH).

Primary outcomes

The incidences of PONV from postoperative days 0 to 1 were the primary outcomes of this study and were assessed by reviewing the medical records. Patient requirement for an additional antiemetic was assessed by the frequency of prescriptions for metoclopramide. We also carried out a subanalysis for the incidences of PONV stratified by risk of PONV (based on the scoring system by Apfel et al.) [7].

Secondary outcomes

A secondary outcome of the study was the postoperative pain assessment as estimated by the Numerical Rating Scale (NRS) on postoperative day 1 at 9:00 during rest. Anesthesiologists informed the patients regarding NRS reporting before surgery and then estimated their postoperative pain using it, during acute pain services (APS) rounds.

The postoperative use of analgesics was another secondary outcome and was assessed by calculating the frequency of prescribed analgesics, including tramadol and

acetaminophen. Data on sex, age, body mass index (BMI), ASA-PS, disease type, maintenance of anesthesia, operation time, LOH, and laboratory results were also collected from the database.

Maintenance of anesthesia

Patients were permitted to drink carbohydrate beverages up to 2 h before administration of anesthesia. No pre-anesthetic medications were administered. Anesthesia was induced with propofol and remifentanil. Following muscle relaxation with rocuronium, the trachea was intubated. Anesthesia was maintained with an inhalation anesthetic (sevoflurane) and remifentanil, and fentanyl and rocuronium were intermittently administered as needed. In both patient groups, IV acetaminophen was injected 30 min before the end of surgery at doses of 1000 mg for patients weighing ≥ 50 kg and 15 mg/kg for patients weighing < 50 kg. Wounds were also infiltrated with a local anesthetic (20–40 ml of 0.2% ropivacaine). After completion of the surgical procedure, remifentanil and inhalation anesthesia were stopped, and muscle relaxation was reversed. Following confirmation of the patient's awakening by an anesthesiologist, the endotracheal tube was removed. Epidural or total IV anesthesia (continuous infusions of propofol and remifentanil) was not utilized for any included surgeries.

Postoperative pain management

Group H

In Group H, postoperative pain medications were administered as needed. When the patient's pain at rest was more than 4 on the NRS, the nurse administered one rescue drug from the medications ordered by the physician. On the day of the procedure, IV infusions of either acetaminophen (Acelio IV Injection; Terumo Corporation, Tokyo, Japan) or tramadol (Tramal IV Injection; Nippon Shinyaku Co., Kyoto, Japan) were used. Starting on postoperative day 1, oral acetaminophen or tramadol was provided as needed, at intervals of 4 h or more. The total maximum tramadol (intravenous or/and oral) used was up to 300 mg per day. NSAIDs were not used for any patients owing to the risk of gastrointestinal complications.

Group S

In Group S, patients were given pain medications at timed intervals, receiving SIVA every 6 h for 24 h postoperatively, for a total of four doses (1000 mg/dose every 6 h for patients weighing ≥ 50 kg and 15 mg/kg every 6 h for patients weighing < 50 kg). Every patient was administered SIVA at the same time (4:00, 10:00, 16:00, and 22:00), unless the first SIVA occurred less than 120 min after surgery ended. On postoperative day 1, patients were switched to scheduled oral acetaminophen. When a patient's pain at rest was over 4 on the NRS, a nurse would administer tramadol at intervals of 4 h or more. Liver function panels were checked on postoperative days 1 and 3. When the levels of AST or ALT were elevated by more than 100 U/L, SIVA was stopped.

Tramadol, a weak opioid, was selected, to relieve visceral pain. NSAIDs were not used in Group S.

Prevention of PONV

In both groups, patients with a high PONV risk (≧60% on the scoring system by Apfel et al.) [7] were given antiemetics during the procedure. Dexamethasone (6.6 mg) was injected following anesthetic induction and droperidol administered (0.625–1.25 mg) at the end of surgery. When PONV occurred, rescue antiemetic therapy with metoclopramide was provided.

Postoperative rehabilitation and nutrition

On postoperative day 1, breathing exercises for 10 min per day were recommended. On postoperative day 2, the patients were advised to be out of bed for more than 2 h. They were permitted to drink clear fluids, starting at 6 h after surgery, and to eat food, starting on the morning of postoperative day 1.

Discharge criteria

Discharge typically occurred on the morning of postoperative day 4 based on the management protocol. Patients were discharged when they met the following criteria: (a) had good pain management with oral analgesia; (b) were able to tolerate solid food without abdominal symptoms; (c) were independently mobile or had the same mobility level as that before admission; and (d) met all of the above criteria and were willing to go home.

Sample size

The sample size was calculated based on the result of a previous study [8]. Based on this study, patients received either acetaminophen 2 g (group A) or placebo (group C) intravenously 30 min while under general anesthesia prior to abdominal hysterectomy. According to the results of this study, the incidence of PONV was lower in group A than in group C (36% vs 60%, $P = 0.044$). Therefore, we estimated that a minimum sample size of 88 patients (44 in each arm) would be needed to obtain 80% power and an alpha level of 0.05 to detect a difference in the incidence of PONV between groups. We set the registration period to 5 months

so that at least 100 patients (50 in each arm) could be registered after allowances for a drop-out of 10%.

Statistical analyses

Statistical analyses were performed using JMP10.0.2 (SAS Institute, Cary, NC, USA).

Group results were compared using Fisher's exact test for binary categorical variables. NRS values, LOH, and the number of prescriptions for antiemetics or analgesics were compared between the two groups using the Wilcoxon rank-sum test and expressed as a median value (minimum value, bottom quartile–top quartile, maximum value). For continuous variables, the results are expressed as a mean value with standard deviation (SD) and compared between groups using a two-sample *t* test. The two-tailed significance level (*P* value) was set at 5%.

Results

Patients who underwent elective LGS during the study period and who met the inclusion and exclusion criteria were selected based on their information in the medical records. All patients were treated according to either the old or the new management protocol during the investigation period. A total of 84 patients were registered for this study, with 34 in Group H and 50 in Group S (Fig. 2). Eighteen patients were dropped from group H: four required no prevention of PONV, eight presented an incomplete set of data, and six were prescribed NSAIDs. Eleven patients were dropped from group S, three did not require prevention of PONV, four presented changes in surgical procedures, and four were prescribed NSAIDs. Table 2 summarizes patient characteristics of both groups. There were no statistically significant differences between the groups regarding age, height, weight, ASA-PS, surgery type, duration of anesthesia, duration of the operations, blood loss, urine volume, intraoperative amounts of administered fentanyl and remifentanil, the end of operation time (AM or PM), or high risk of PONV.

Primary outcomes

The incidences of PONV from postoperative days 0 to 1 were significantly lower in Group S than in Group H (Group H = 58.8%, Group S = 30.0%, $P = 0.0085$) (Table 3). Furthermore, the frequency of metoclopramide prescriptions from postoperative days 0 to 1 was significantly lower in Group S than in Group H (Group S: 0 [0, 0–1.0, 2.0]; Group H: 2.0 [0, 1.0–4.0, 7.0]; $P = 0.0129$) (Fig. 3). The incidence of PONV was significantly higher in patients with a low PONV risk (Apfel score = 0–2 points) in Group H than those in group S (Group H: 60.0%; Group S: 17.4%; $P = 0.0054$) (Table 4).

Secondary outcomes

Figure 4a compares the NRS at rest on postoperative day 1 at 9:00 in both groups. The NRS did not significantly differ between patients both groups (Group S: 2 [0, 0–3.0, 8.0]; Group H: 1.0 [0, 0–1.0, 4.0]; $P = 0.1947$). The number of additional tramadol prescriptions from postoperative days 0 to 1 was significantly lower in Group S than in Group H (Group S: 0 [0, 0–1.0, 2.0]; Group H: 1.0 [0, 0–2.0, 4.0]; $P = 0.0021$) (Fig. 4b). LOH after surgery did not significantly differ between the groups (Group S: 4.0 [3.0, 4.0–4.0, 5.0] days; Group H: 4.0 [3.0, 4.0–4.0, 5.0] days; $P = 0.0552$) (Table 5). No patient in either group had an elevation of more than 100 U/l in their AST or ALT levels on postoperative day 1.

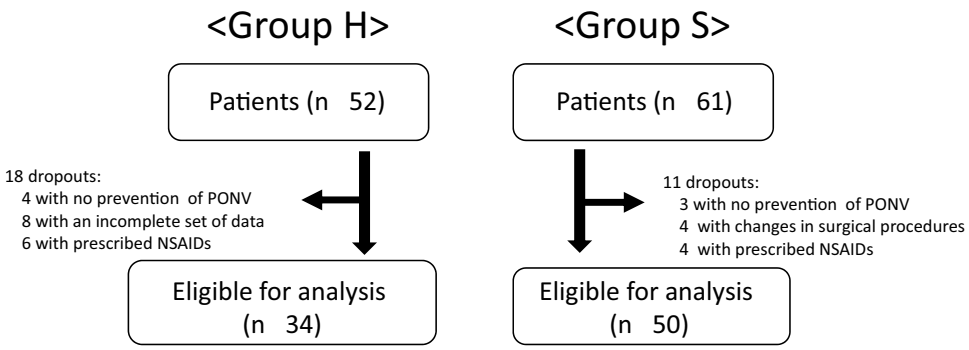

Fig. 2 Flowchart of eligible patients. In total, 84 patients were eligible for analysis, including 34 patients in Group H and 50 patients in Group S. In Group H, 12 patients were excluded: four patients did not receive PONV prophylaxis during surgery and eight patients had incomplete datasets. In Group S, seven patients were excluded: three patients did not receive PONV prophylaxis during surgery and four patients had changes in their surgical procedures

Table 2 Patient characteristics

	Group H ($n=34$)	Group S ($n=50$)	P value
Age (years)	44.7 ± 11.2	42.7 ± 11.8	0.4464*
Height (cm)	157.8 ± 6.7	158.6 ± 5.4	0.5500*
Weight (kg)	55.2 ± 7.3	57.6 ± 12.4	0.3001*
ASA-PS score			0.4077
I (n)	20	34	
II (n)	12	16	
III (n)	1	0	
Surgery type			0.2876††
Laparoscopic hysterectomy (n)	13 (38.2%)	25 (50.0%)	
Laparoscopic ovarian resection (n)	21 (61.8%)	25 (50.0%)	
During operation			
Anesthetic duration (min)	166.4 ± 44.3	175.2 ± 54.0	0.4335*
Operative duration (min)	121.6 ± 42.6	132.4 ± 54.4	0.3362*
The end of operation time (AM(n)/PM(n))	20/14	33/17	0.5043††
Fentanyl (μg)	341 ± 108	354 ± 103	0.5847*
Remifentanil (mg)	0.84 ± 0.21	0.86 ± 0.29	0.8018*
Blood loss (ml)	33 [0, 112.5]	20 [0, 80.5]	0.5578†
Urine volume (ml)	135 [100, 300]	200 [95, 400]	0.6456†
Patients with high PONV risk (n)	14 (41.2%)	27 (54.0%)	0.2485††

Continuous variables: mean ± standard deviation; Group H: historical group; Group S: SIVA group; Patients with a high PONV risk: ≧60% on scoring system by Apfel et al. [7]

Mean value ± standard deviation, median value [first quartile, third quartile]

*A two-sample t test: significant when $P<0.05$

†Wilcoxon rank-sum test: significant when $P<0.05$

††Fisher exact probability test: significant when $P<0.05$

Table 3 Incidence of PONV

	Group H ($n=34$)	Group S ($n=50$)	P value
PONV (+): n (%)	20 (58.8%)	15 (30.0%)	0.0085*
PONV (−): n (%)	14 (41.2%)	35 (70.0%)	

PONV postoperative nausea and vomiting

*Fisher's exact probability test: significant when $P<0.05$

Discussion

This study showed that postoperative SIVA in patients undergoing LGS significantly reduced the incidences of both PONV. SIVA also significantly reduced the number of required prescriptions for metoclopramide from postoperative days 0 to 1. When stratified according to initial risk for PONV, the incidence of PONV was significantly lower in patients with a low-PONV-risk in Group S than in those in Group H. Furthermore, postoperative SIVA significantly reduced the required number of rescue analgesic medications (i.e., tramadol). However, the NRS at rest on postoperative day 1 at 9:00 and the LOH did not differ between the two groups.

PONV occurs in approximately 30% of patients undergoing general anesthesia [7, 9]. Female gender, nonsmoking status, a history of PONV and/or motion sickness, and anticipated use of postoperative opioids have previously been identified as important risk factors for PONV [7, 9]. Apfel et al. have demonstrated that cholecystectomies, laparoscopic procedures, and gynecological surgeries are also statistically significant independent predictors of PONV [7]. Furthermore, antiemetics such as 5-HT3 receptor antagonists and neurokinin-1 (NK1) receptor antagonists are still unapproved for use in Japan. These factors may explain the high incidence of PONV in both Group H (58.8%) and Group S (30.0%) patients, which necessitated the use of the weak opioid tramadol, especially in Group H.

It has been well documented that opioid analgesics are associated with nausea, vomiting, sedation, dysphoria, pruritus, constipation, urinary hesitancy, and respiratory depression after surgery [10]. If our hospital's protocol had allowed physicians to use ondansetron in patients, then the incidence of PONV identified in this study might have been decreased, as observed in other studies of laparoscopic cholecystectomies [11, 12]. However, as physicians could not use ondansetron, the incidences of PONV were significantly decreased by the administration of postoperative SIVA, allowing for

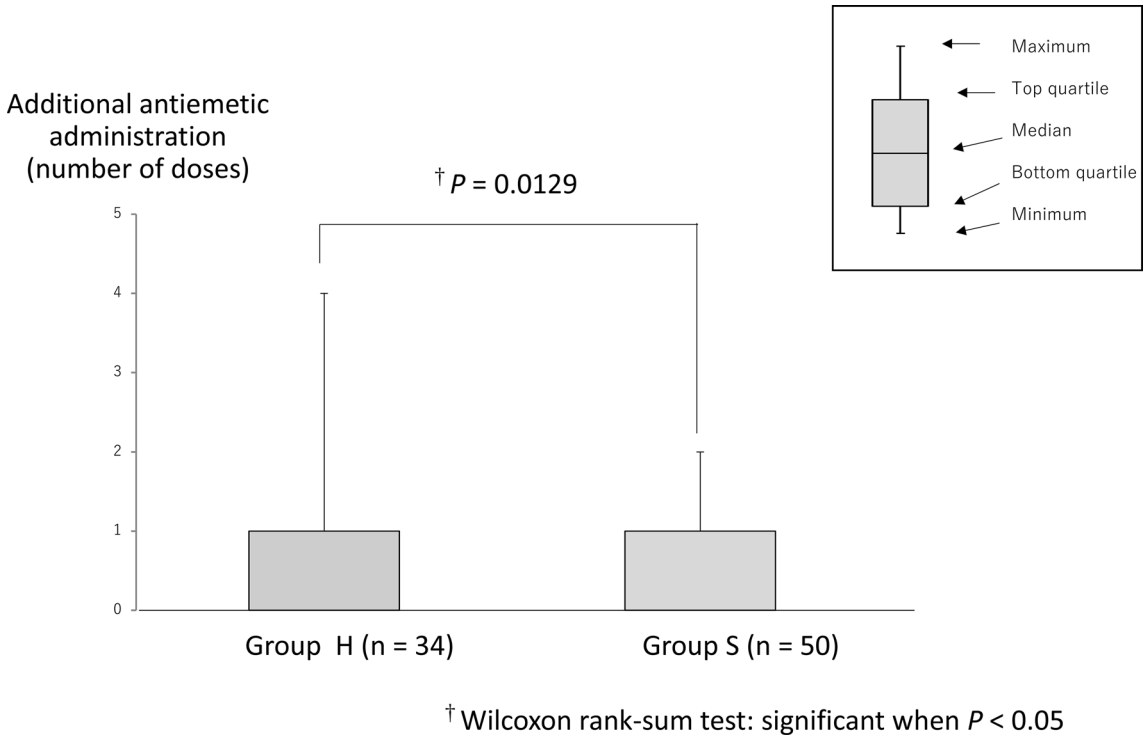

Fig. 3 The number of additional antiemetics required from postoperative days 0 to 1. The number of additional antiemetics required from postoperative days 0 to 1 was significantly lower in Group S than in Group H [Group S: 0 (0, 0–1.0, 2.0); Group H: 2.0 (0, 1.0–4.0, 7.0); $P = 0.0129$]. The number of antiemetic prescriptions was compared between groups using a Wilcoxon rank-sum test and expressed as a median value (minimum value, bottom quartile to top quartile, maximum value)

Table 4 Incidence of PONV according to high or low risk for PONV

	PONV (+)	PONV (−)	Total
Low PONV risk: Apfel score = 0–2 points			
Group H: *n* (%)	12 (60.0%)	8 (40.0%)	20
Group S: *n* (%)	4 (17.4%)*	19 (82.6%)	23
			*$P = 0.0054$
High PONV risk: Apfel score = 3–4 points			
Group H: *n* (%)	8 (57.1%)	6 (42.9%)	14
Group S: *n* (%)	11 (40.7%)	16 (59.3%)	27
			$P = 0.3458$

Patients with high PONV risk: ≧60%; scoring system by Apfel et al. [7]

PONV postoperative nausea and vomiting

*Fisher's exact probability test: significant when $P < 0.05$

scarce opioid administration and a decreased need for tramadol. Apfel et al. found similar results and concluded that PONV prophylaxis is rarely warranted in low-risk patients, while moderate-risk patients may benefit from a single intervention [6]. Additionally, Apfel et al. recommended that multiple interventions should be reserved only for high-risk patients because antiemetics are highly effective, safe, and inexpensive. In contrast, our study shows that even patients with a low risk of PONV can benefit from postoperative SIVA, as the incidence of PONV was significantly lower in Group S patients than in Group H patients [6]. Therefore, we conclude that prophylaxis of PONV using antiemetics should be prescribed according to PONV risk; however, SIVA prophylaxis should be used regardless of the assessed risk grade.

The postoperative pain management protocol utilized in Group S was based on a number of historically important studies and guidelines. In 2002, Crews et al. showed that a

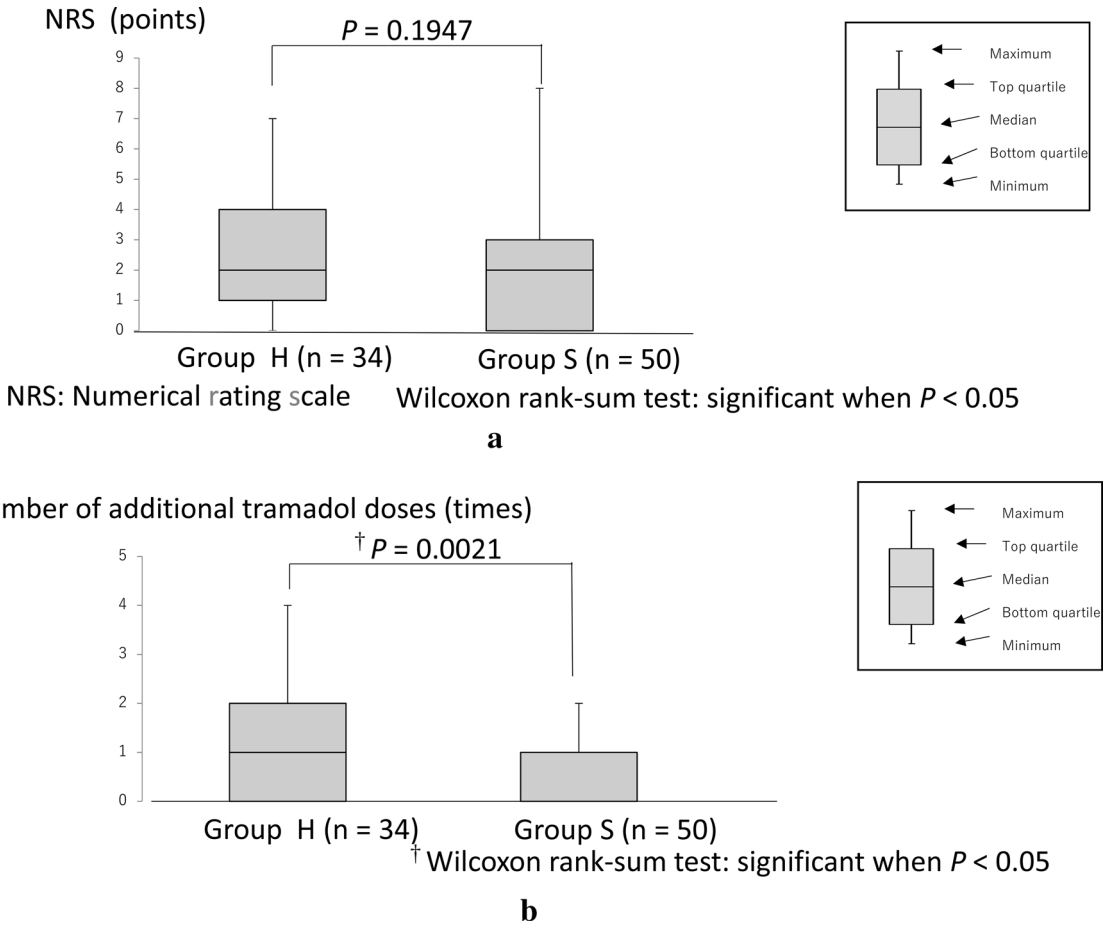

Fig. 4 **a** The NRS at rest on postoperative day 1 at 9:00. The NRS did not significantly differ between groups (Group S: 2 [0, 0–3.0, 8.0]; Group H: 1.0 [0, 0–1.0, 4.0]; $P=0.1947$). The NRS was compared between groups using a Wilcoxon rank-sum test and expressed as a median value (minimum value, bottom quartile to top quartile, maximum value). **b** The number of prescriptions for tramadol from postoperative days 0 to 1. The number of tramadol prescriptions from postoperative days 0 to 1 were significantly lower in Group S than in Group H [Group S: 0 (0, 0–1.0, 2.0); Group H: 1.0 (0, 0–2.0, 4.0); $P=0.0021$]. The number of tramadol prescriptions were compared between the groups using the Wilcoxon rank-sum test and expressed as a median value (minimum value, bottom quartile to top quartile, maximum value)

Table 5 Length of hospitalization after surgery

	Group H ($n=34$)	Group S ($n=50$)	P
LOH after surgery (days)	4.0 [3.0, 4.0–4.0, 5.0]	4.0 [3.0, 4.0–4.0, 5.0]	0.0552

Wilcoxon rank-sum test: significant when $P<0.05$

Median value [minimum value, bottom quartile to top quartile, maximum value]

LOH length of hospitalization

multimodal strategy for the management of postoperative pain should be pursued in a stepwise manner [13], similar to the ladder of therapy for cancer pain developed by the World Health Organization [14]. As a result, the postoperative pain management protocols in our hospital were designed to incorporate that stepwise model. Further, the ERAS protocol for pain management after gastrointestinal surgeries recommends a multimodal analgesia (MMA) regimen, including the administration of opioids, non-opioids, epidural anesthesia, and local anesthesia [15]. The MMA regimen is based on the routine use of non-opioid analgesia (i.e., NSAIDs, COX-2 inhibitors, and acetaminophen) and is indicated in patients undergoing open and laparoscopic abdominal procedures. This regimen is designed to reduce the consumption of opioids and their dose-dependent side effects, which are known to delay recovery. As our study analyzed patients who underwent an LGS for benign diseases, a combination of treatment with non-opioid medications and

local anesthetic wound infiltration was selected for postoperative pain management. In this study, we evaluated the NRS on a postoperative day 1 at 9:00 to assess the effects of acetaminophen at minimum blood and cerebrospinal fluid (CSF) concentrations, as every patient received SIVA at the same timepoints (4:00, 10:00, 16:00, 22:00) in our hospital. We believe that the reason the NRS and the number of doses of rescue medicines (i.e., tramadol) administered during the first 24 h after surgery were lower in Group S than in Group H was that CSF concentration of acetaminophen was maintained by SIVA. Neil et al. demonstrated that earlier and greater CSF penetration occurs as a result of the earlier and higher plasma peak levels achieved with IV acetaminophen administration than with oral or rectal administration [16]. Other studies have confirmed that IV acetaminophen reaches a higher and faster peak plasma concentration than oral administration [17]. SIVA has repeatedly been shown to be a safe and efficacious analgesic in major orthopedic surgeries [18, 19]. Similarly, it has been found to be efficacious for gastrointestinal and gynecological surgeries [20, 21]. Even if the number of rescue medicines administered during the first 24 h after surgery was significantly lower in Group S, the NRS score did not significantly differ between Groups H and S. We speculate that no significant differences were identified due to LGS being a less invasive procedure with lower associated pain levels.

Santoso et al. demonstrated that multimodal pain control is associated with a significant reduction in LOH following open abdominal hysterectomy [22]. Similarly, Shaffer et al. demonstrated that pairing SIVA with opioid use for postoperative pain management could potentially decrease LOH, opioid-related complication rates, and hospital expenses [23]. The updated ERAS Society guidelines for gynecologic/oncology surgery also support this point of view [3]. Our results show, however, that LOH following surgery did not differ between Group H and Group S patients. This discrepancy may result from a unique feature of the Japanese medical system, i.e., the Diagnosis Procedure Combination/Per-Diem Payment System (DPC/PDPS). In Japan, the amount of a medical fee is the sum of a comprehensive evaluation and a high evaluation component, which is predetermined for each DPC. Therefore, LOH is not an accurate index for medical economic burdens. As the LOH of LGS is initially shorter, a significant difference may have been difficult to identify, even with the use of a weak opioid versus a stronger one.

This study had several limitations. First, because of the small sample size in the control group, the total quantity of tramadol used was significantly higher; therefore, it might have seemed to contribute to PONV and bias the result. However, we do not consider it excessive, as the amount of intravenous tramadol was administered in up to three doses (100 mg per time) per day. We evaluated the generating frequency of PONV that occurs in the range of the usual amount used and concluded that the study involved limited bias.

Second, because the evaluation of PONV was carried out by different nurses, it is possible that the assessments were inconsistent. Further, as evaluation of PONV cannot be carried out quantitatively, there is a limit to its utility, especially in a retrospective study. In contrast, we could have quantitatively evaluated the number of additional antiemetics used and thereby assessed for PONV and the effect of SIVA appropriately. Third, we used only one evaluation time-point for the NRS instead of an average of scores at several times, which would have been ideal. Furthermore, the NRS was evaluated only during rest, when ideally; it should have been evaluated also while the patients were mobile. However, as the NRS was directly evaluated by the same anesthesiologist, the accuracy of its evaluation was considered high.

Conclusion

Introduction of SIVA into the postoperative pain management protocol of LGS reduced the incidences of PONV, and the number of prescriptions for adjunctive antiemetics from postoperative days 0 to 1. The incidence of PONV in patients who were considered to have a low risk of PONV was significantly lower in Group S than in Group H. Furthermore, postoperative SIVA reduced the number of times rescue analgesic medications were required. The NRS at rest on postoperative day 1 at 9:00 and the LOH did not differ between the groups. In patients undergoing LGS, PONV prophylaxis using antiemetic medications should be prescribed according to the PONV risk assessment; however, PONV prophylaxis using SIVA can be used regardless of an individual's risk assessment. Our results suggest that SIVA can be introduced into the management protocols of multiple procedures in Japan.

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Author contribution TS and TU contributed to the study conception and the designing and drafting of the manuscript. MN and TK contributed to acquisition and interpretation of the data. TY was responsible for the revision of important intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest in this work.

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