Clinical Trial/Experimental Study

Medicine

OPEN

A randomized controlled trial comparing incidences of postoperative nausea and vomiting after laparoscopic cholecystectomy for preoperative intravenous fluid loading, ondansetron, and control groups in a regional hospital setting in a developing country

Mingkwan Wongyingsinn, MD[a], Pechprapa Peanpanich, MD[a,b], Sirirat Charoensawan, MD[b]

Abstract

Background: Postoperative nausea and vomiting (PONV) is a common complication in inpatient and outpatient settings. Multimodal approaches have been pursued to minimize this undesirable outcome. Despite consensus guidelines for the management of PONV have been updated and published for many years, data from our pilot study showed that patients with high-risk surgeries for PONV, laparoscopic cholecystectomy (LC), still hardly received perioperative PONV prophylaxis. This study aimed to compare the incidences of PONV in adult patients undergoing elective LC who were administered preoperative intravenous fluid loading, ondansetron, or neither fluid nor ondansetron in the setting of a regional hospital in a developing country.

Methods: The study was designed as a prospective randomized controlled trial. The total of 171 patients was allocated to three groups: one received fluid loading with Ringer's lactate solution before the operation; the second received ondansetron; and the third group received neither.

Results: In total, 156 patients were analyzed. Their demographic data, history of motion sickness/PONV, and smoking status were not significantly different. The overall incidences of PONV within 24 hours of surgery were 29.1% in the fluid group, 18.4% in the ondansetron group, and 25% in the control group, but the difference was not statistically significant (P = .442). In subgroup analysis, the incidences of PONV and PON in patients younger than 50 years old were significantly different among the three groups (P = .008). A post hoc analysis showed that patients under 50 years in the ondansetron group had significantly lower incidences of PONV and PON than those in the control and fluid groups. However, the incidences of morphine consumption and dizziness in the ondansetron group were significantly higher than those of the two other groups.

Conclusions: Neither the preoperative intravenous fluid loading nor the ondansetron affected PONV in patients aged 50 and older undergoing LC, compared with control. Ondansetron was beneficial for PON prophylaxis in patients under the age of 50, whereas preoperative intravenous fluid loading was considered a risk factor for PON in this population.

Abbreviations: 5-HT3 = 5-hydroxytryptamine, ASA = American Society of Anesthesiologists, IQR = interquartile range, LC = laparoscopic cholecystectomy, NSAIDs = non-steroidal anti-inflammatory drugs, PON = postoperative nausea, PONV = postoperative nausea and vomiting, POV = postoperative vomiting, SD = standard deviation, VRS = verbal rating score.

Keywords: fluid therapy, laparoscopic cholecystectomy, ondansetron, postoperative nausea and vomiting

1. Introduction

Multiple advances have been made in the last decade toward minimizing adverse outcomes after surgery and anesthesia; however, nausea and vomiting remain one of the most undesirable postoperative outcomes.[1,2] Many effects are related to postoperative nausea and vomiting (PONV), including suture dehiscence, aspiration of gastric contents, and esophageal rupture.[2–4] The incidence of PONV varies considerably in both inpatient and outpatient settings. The incidence of postoperative nausea

This study was supported by the Royal College of Anesthesiologists of Thailand.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [b] Department of Anesthesiology, Buddhachinaraj Phitsanulok Hospital, Phitsanulok, Thailand.

** Correspondence: Mingkwan Wongyingsinn, Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand (e-mail: mingkwan.won@mahidol.ac.th).*

How to cite this article: Wongyingsinn M, Peanpanich P, Charoensawan S. A randomized controlled trial comparing incidences of postoperative nausea and vomiting after laparoscopic cholecystectomy for preoperative intravenous fluid loading, ondansetron, and control groups in a regional hospital setting in a developing country. Medicine 2022;101:42(e31155).

Received: 16 June 2022 / Received in final form: 12 September 2022 / Accepted: 14 September 2022

http://dx.doi.org/10.1097/MD.0000000000031155

(PON) alone ranges from 20% to 40%,[2] while that of postoperative vomiting (POV) ranges from 12% to 25%.[2,5]As to PONV, its incidence ranges from 25% to 30% for general surgery,[2,5,6] and it has been found to reach 60–70% in high-risk patients.[2,5] High-risk patients include those of the female gender, nonsmokers, postoperative opioid users, and those with a history of PONV or motion sickness.[1,3] Additionally, laparoscopic surgery is a surgical risk factor for PONV.[7] Its incidence after laparoscopic cholecystectomy (LC) is higher than for other types of surgery, with reports of 46% to 75% for patients who did not receive antiemetic treatment.[2,6,8]

The most recent consensus guidelines for the management of PONV, published in 2020, recommend the use of an antiemetic combination strategy and a multimodal prevention approach to prevent and treat PONV in clinical settings.[1] The first-line recommended pharmacological antiemetic for use as PONV prophylaxis in adults is a 5-hydroxytryptamine (5-HT3) receptor antagonist.[1,2] It affects the chemoreceptor trigger zone and vagal afferents in the gastrointestinal tract,[9] and it is considered to be very effective for PONV management. Nevertheless, there are some drug-related adverse events, including headache, increased liver enzymes, constipation,[9] extrapyramidal reactions, seizure,[10] anaphylaxis,[11] and cardiac arrhythmia.[10] These prolong hospitalization and increase treatment costs.[9–11]

Since 2010, several studies have demonstrated that the use of a preoperative higher volume hydration protocol can significantly reduce the incidence of PONV and is cost-effective in the absence of prophylactic antiemetic therapy.[12–17] The mechanism is unclear. However, it has been postulated that fluid loading before the induction of anesthesia most probably reduces the volume deficit, bringing a patient closer to normovolemia and decreasing intestinal hypoperfusion. The fluid loading may also be related to a reduced release of serotonin.[9,12,15] A systematic review in 2012 suggested that an intravenous crystalloid supplement was associated with a lower incidence of several PON outcomes.[14] Still, some POV and PONV outcomes failed to reach statistical significance, which might have been because of a lack of statistical power.[14]

Despite the fact that a consensus management guideline for PONV has been updated and published for many years, a pilot study in our hospital demonstrated that patients barely received PONV prophylaxis even with high PONV risk surgery such as a LC. The main reasons were that there was no PONV prophylaxis protocol in our hospital and anesthetists were not aware of risk factors for PONV, respectively. Our pilot study showed an incidence of PONV in patients undergoing LC with no PONV prophylaxis approximately 35%. This trial hypothesized that the incidences for patients receiving preoperative intravenous fluid loading and those administered ondansetron would be statistically lower than that for patients not given fluid or ondansetron; however, both incidences were expected to be not statistically different. PONV incidences were compared in three patient groups after elective LC: those who received preoperative intravenous fluid loading, those who received ondansetron, and those who received neither fluid nor ondansetron.

2. Materials and Methods

This prospective randomized controlled study was registered at ClinicalTrials.gov (NCT03141645; 05/05/2017). Ethics approval was obtained from the Siriraj Institutional Review Board (Si491/2017) and Buddhachinaraj Institutional Review Board (074/60). All methods were carried out following relevant guidelines and regulations. Each participant was informed about the study protocol in detail and signed an informed consent form before enrollment by one of the authors. The inclusion criteria were patients undergoing elective LC at Buddhachinaraj Hospital between June 2017 and August 2018, aged 18 to 70 years, and the American Society of Anesthesiologists (ASA) physical status of 1 to 3. Patients were excluded if they were pregnant or breast-feeding; had taken antiemetic drugs during the 24 hours preceding the surgery; were hypersensitive to ondansetron; had chronic kidney disease (stages 4–5), congestive heart failure, valvular heart disease, a left ventricular ejection fraction < 40, or cirrhosis (Child-Pugh score C); declined to participate; could not communicate; or were unable to comprehend the purpose of the study. In addition, if the surgery was converted to another operation, the patient concerned was automatically dropped from the study. The study recruitment was stopped when the sample size goal has been reached.

2.1. Hospital and setting

Our hospital, Buddhachinaraj Phitsanulok hospital, is classified as a regional hospital in Phitsanulok province and under the Ministry of Public Health, Thailand. It has a collaborative project to increase the production of rural doctors and is an affiliated teaching hospital of the Faculty of Medicine Siriraj Hospital, Mahidol University. General anesthesia in our hospital has been done without a routine PONV prophylaxis. Anesthesiologists and nurse anesthetists can administer medications for PONV prophylaxis by their preference; including drug, dose, and using a single drug or combination therapy.

2.2. Randomization and study groups

Using computer-generated assignment by an investigator with no clinical involvement in the trial, the patients were randomly allocated following blocked randomization procedures (using a block size of 9) to one of three study groups: a fluid group, an ondansetron group, and a control group. The allocation sequence was concealed from the researcher enrolling and assessing patients in sequentially numbered, opaque, sealed, and stapled envelopes. The details of the allocated sequence were unknown to other investigators. After induction of anesthesia, the appropriate numbered envelope was opened at the operation theater; and this information was then given to the anesthesia team who anesthetizes the participants. Whereas anesthesiologists were aware of the allocated arm; patients, outcome assessors, and data analysts were kept blinded to the allocation throughout the study period.

The patients in the fluid group received Ringer's lactate solution (10 mL/kg) for 15 minutes before the commencement of their operation. In the ondansetron group, patients were intravenously administered ondansetron (8 mg) for 15 minutes before the end of the operation. In contrast, the control group patients did not receive either preoperative intravenous fluid loading or intravenous ondansetron.

2.3. Anesthesia and analgesia

On the night before surgery, the patients were not allowed to consume any food or drink after midnight. After that time, they were administered an intravenous solution with 5% dextrose in normal saline at a maintenance rate. Standard general anesthesia and orotracheal intubation were applied to all patients. General anesthesia was initiated with a 100% preoxygenation and induced with intravenous fentanyl (1 mcg/kg), propofol (1.5–2 mg/kg), and succinylcholine (1–1.5 mg/kg). After orotracheal intubation was achieved, cisatracurium was provided as a muscle relaxant and maintained every 30 minutes during surgery. The ventilator setting was initially set at 8 mL/kg of tidal volume, and the respiratory rate at 12 breaths per minute, with an inspiratory: expiratory ratio of 1:2 and a positive-end expiratory pressure of 5. The ventilator setting was adjusted to maintain intraoperative normocarbia. The anesthesia was maintained with sevoflurane in a mixture of air and oxygen (50% each), with the end-tidal concentration of sevoflurane adjusted to keep it at 0.8–1.0 MAC. The intraoperative

standard monitoring included electrocardiography, heart rate, noninvasive blood pressure, oxygen saturation, end-tidal carbon dioxide, end-tidal gas, and core temperature. A thermal blanket was positioned over the exposed parts of the body to maintain perioperative normothermia. Supplemental doses of fentanyl (25 mcg) were administered if either the intraoperative blood pressure or the heart rate exceeded the baseline value by 20%. Hypotension - defined as a blood pressure <20% of the baseline value - was treated with intravenous norepinephrine or ephedrine. Bradycardia, defined as a heart rate <60 beats per minute and/or a rapidly falling heart rate, was treated with intravenous atropine. All patients received an intravenous infusion of Ringer's lactate solution at a maintenance rate determined with the Holliday–Segar method.

The postoperative analgesia was assessed with a verbal rating score (VRS; 0 = no pain, 10 = worst pain) at rest in the post-anesthesia care unit (PACU) and on the surgical ward. If the VRS pain at rest was >3, the patient was given intravenous morphine (3 mg). All patients received multimodal analgesia with paracetamol and NSAIDs (non-steroidal anti-inflammatory drugs) (if no contraindication) around the clock.

2.4. Surgical technique

Intravenous prophylactic antibiotics were administered to every patient. All operations were performed by well-experienced surgeons (with at least 3 years' experience in LC). Pneumoperitoneum was created by CO_2 insufflation performed by the surgeon. Intraoperatively, the intraabdominal pressure was maintained at 8 to 16 mm Hg by an automatic insufflator and a nasogastric tube was not routinely retained.

2.5. Data collection and outcome measures

Patients' demographic data and intraoperative data were immediately collected after the end of the operation. Postoperative data were collected from the patients' charts and entered on a case-record form by one of the authors or a research assistant who was kept blinded to the allocation and intraoperative data. Additionally, all patients were blinded throughout the study period. The postoperative care pathway was followed as per routine by ward nurses, and postoperative complications of anesthesia were evaluated by anesthesia teams during their postoperative rounds. Patients had no restrictions on activities, and they were encouraged to resume work and normal daily activities as soon as possible. They were discharged as per the usual practices at Buddhachinaraj Hospital.

The following data were collected: demographic characteristics; duration of surgery; conversion rate to other operations; the amount of preoperative fluid administration (defined as the volume of intravenous fluid administered from the commencement of fasting to the start of the operation); the volume of intraoperative fluid administered; estimated blood loss during the operation; the intraoperative and postoperative usage and amounts of analgesic medications; the quality of pain relief; the incidence of PON, POV and PONV in the first 24-hour postoperative period; the treatment of PON, POV and PONV including conservative treatment and pharmacological treatment; side effects related to fluid loading and ondansetron; intraoperative and postoperative complications; and length of postoperative hospital stay. The side effects related to fluid loading comprised urinary retention requiring catheterization, volume overload, and congestive heart failure; those related to ondansetron were headache, dizziness, extrapyramidal reactions, and cardiac arrhythmia.

The primary outcome of this study was the PONV incidence for the 24 hours following the operation. The secondary outcomes were the length of hospital stay after the operation, the incidence of side effects related to fluid loading and ondansetron, and other postoperative complications.

2.6. Sample size calculation and statistical analysis

The sample size calculation was based on a pilot study in our hospital and the other two studies.[8,15] The pilot study demonstrated a PONV incidence of approximately 50% in patients who did not receive either preoperative intravenous fluid loading or intravenous ondansetron as routine care in our hospital. A study by Liberman et al showed ondansetron decreases the incidence of PONV from 66% to 40% with placebo;[8] while a study by Lambert et al demonstrated patients receiving a preoperative fluid bolus experienced a lower incidence of PONV than patients receiving a routine amount of intravenous fluid administration (22% vs. 52%).[15] It used nQuery Advisor (version 7.0; Statistical Solutions Ltd., Cork, Ireland) to detect a reduction in the primary outcomes of the 2 intervention groups (25%) relative to the control group (50%), with a type I error of 0.05 and a power of 80%. After allowing for a 10% dropout, the sample size was 57 patients for each group.

Categorical data are presented as the number of patients and proportions, and comparisons between the groups used the Chi-squared test. Continuous parametric data are tested for normality and presented as mean ± standard deviation (SD), or median (interquartile range; IQR) as appropriate. Comparisons between the groups used ANOVA or a Kruskal–Wallis test, with a post hoc analysis as appropriate; and a *P*-value <.050 was considered significant. The statistical analyses were performed using IBM SPSS Statistics for Windows (version 21.0; IBM Corp., Armonk, NY).

3. Results

Of the 269 patients enrolled in this study, 171 patients were randomized. Fifteen patients were converted from the laparoscopic technique to an open cholecystectomy, leaving a total of 156 patients for the final analysis (Fig. 1). Table 1 details the patient characteristics (gender, age, body mass index, ASA physical status, underlying diseases, smoking status, and a history of motion sickness and/or PONV). The data of the 3 groups were not statistically different ($P > .050$).

There were also no significant differences in the intraoperative data of the 3 groups (duration of surgery, amount of intraoperative fentanyl, estimated blood loss, and incidences of hypotension and bradycardia; $P > .05$). All patients underwent reversal of neuromuscular blocking agents at the end of surgery with neostigmine 2.5 mg and atropine 1.2 mg intravenously. The volumes of preoperative intravenous fluid administered before entering the operating theater to the 3 groups were similar. However, the fluid administration inside the operating theater for the fluid group (908 ml ± 283 mL) was significantly higher than that for the ondansetron group (390 mL ± 141 mL; $P < .001$) and the control group (333 mL ± 102 mL; $P < .001$; Table 2).

The incidences of PONV and PON were 16 patients (29.1%, 95% CI 17.6-42.9%) in the fluid group, 9 patients (18.4%, 95% CI 8.8-32%) in the ondansetron group, and 13 patients (25%, 95% CI 14-38.9%) in the control group, with no statistically significant difference ($P = .442$). Furthermore, the incidences of POV in the three groups were comparable ($P = .353$; Table 3). We further explored the incidences between age subgroups (<50, and ≥50 years). The incidences of PONV and PON in patients younger than 50 years old were significantly different among three groups ($P = .008$ and $P = .008$, respectively; Table 4). Additionally, no patients under the age of 50 in the ondansetron group reported experiencing nausea and/or vomiting after surgery. A post hoc analysis showed that patients under 50 years in the ondansetron group had significantly lower incidences of PONV and PON than those in the control and fluid groups (0% vs 30% and 38.5%, $P < .050$).

Seven patients (5 from the control group, and 2 from the ondansetron group) required a conservative treatment such as

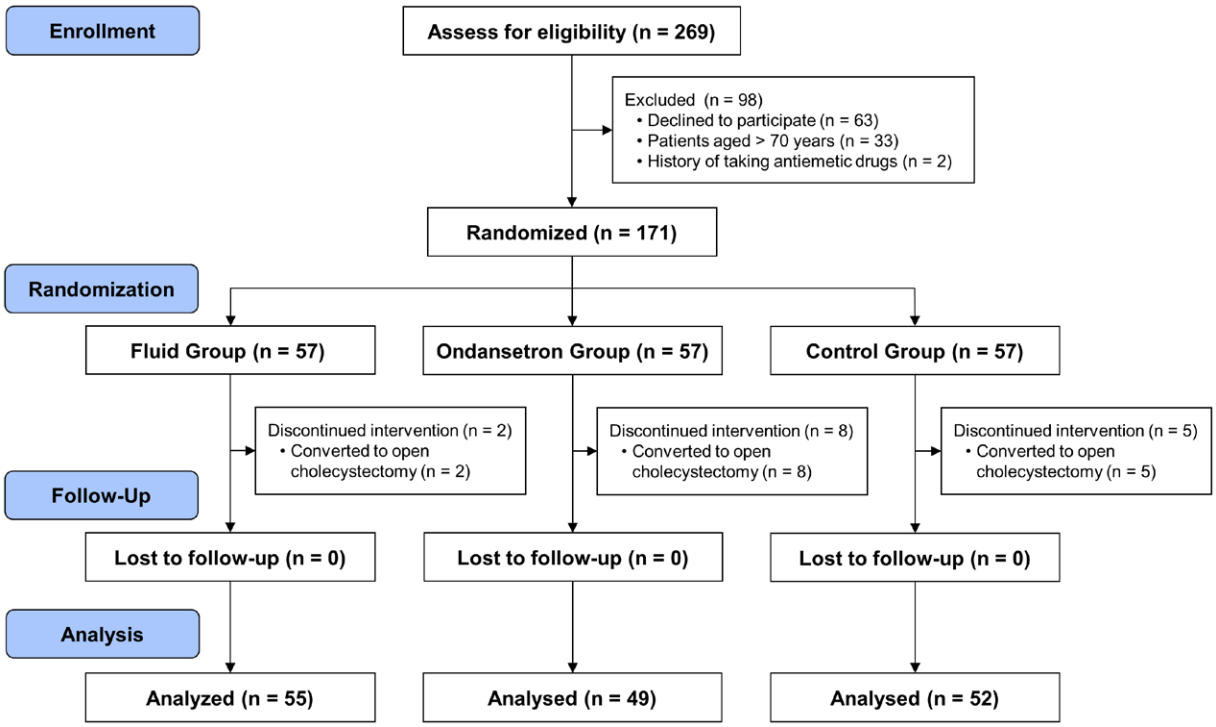

Figure 1. Consort flow diagram.

Table 1

Demographic characteristics.

	Fluid group (n = 55)	Ondansetron group (n = 49)	Control group (n = 52)	*P* value
Female	40 (72.7)	33 (67.3)	37 (71.2)	.829
Age (years)	49 ± 11	51 ± 12	51 ± 13	.661
Age < 50 years	26 (47.3)	20 (40.8)	20 (38.5)	.633
Body mass index (kg/m^2)	26.1 ± 4.8	25.5 ± 3.9	25.9 ± 5.1	.775
ASA physical status				.126
I	18 (32.7)	19 (38.8)	13 (25)	
II	36 (65.5)	27 (55.1)	32 (61.5)	
III	1 (1.8)	3 (6.1)	7 (13.5)	
Underlying diseases				
Hypertension	12 (21.8)	11 (22.4)	21 (40.4)	.057
Dyslipidemia	14 (25.5)	7 (14.6)	10 (19.2)	.382
Diabetic Mellitus	4 (7.3)	5 (10.2)	8 (15.4)	.397
Anemia	3 (5.5)	2 (4.1)	6 (11.5)	.291
Smoker	11 (20)	7 (14.3)	6 (11.5)	.464
History of motion sickness and/or PONV	2 (3.6)	2 (4.1)	6 (11.5)	.180

Data are presented as number (percentage) or mean ± standard deviation.
Comparisons between the groups used Chi-squared or ANOVA test.
A *P*-value < .05 is considered statistically significant.
ASA = the American Society of Anesthesiologists classification, PONV = postoperative nausea and vomiting.

taking deep breaths, ammonia or aroma inhalant, or placing a cool compress on the forehead. All 16 PONV patients (100%) in the fluid group required pharmacological treatment, compared with 6/9 patients (66.7%) in the ondansetron group and 8/13 patients (61.5%) in the control group who needed that treatment (P = .028). Four patients (two from the ondansetron group, and one each from the fluid and control groups) required a pharmacological combination therapy, in which they were administered more than one antiemetic drug. The antiemetic drugs of choice were metoclopramide and domperidone.

Moving on to postoperative pain and analgesia, both the scores for postoperative pain and the morphine requirements of the 3 groups were comparable (P = .650 and .560, respectively). Dizziness was the only postoperative adverse event that differed significantly between the three groups (P = .028). While more of the ondansetron patients experienced dizziness (16.3%) than those receiving fluid (1.8%), the incidence for the ondansetron group was not significantly different from the incidence for the control group (7.7%). There were no reported cases of cardiac arrhythmia, congestive heart failure, or extrapyramidal symptoms. The lengths of postoperative hospital stay for the 3 groups were identical (2 days).

4. Discussion

PONV is a common reason for discharge delay and readmission, especially for ambulatory surgery.[18,19] Regarding consensus guidelines, ondansetron is considered to be the gold-standard

Table 2

Intraoperative data.

	Fluid group (n = 55)	Ondansetron group (n = 49)	Control group (n = 52)	*P* value
Operative time (min)	118 ± 41	124 ± 58	105 ± 27	.084
Amount of fentanyl (mcg)[k]	100 [100, 125]	100 [100, 125]	100 [100,107.5]	.656
Intravenous fluid administration (mL)				
Before entering the operating theater[a]	255 ± 130	240 ± 115	240 ± 130	.747
Inside the operating theater[a]	908 ± 283*,**	390 ± 141*	333 ± 102**	<.001
Estimated blood loss (mL)[a]	5 [5, 20]	10 [5, 20]	7.5 [5, 20]	.756
Number of patients with:				
Hypotension	12 (21.8)	4 (8.2)	5 (9.6)	.077
Bradycardia	1 (1.8)	5 (10.2)	3 (5.8)	.187

Data are presented as mean ± standard deviation, median [IQR], or number (percentage).

a Comparison between the groups used an ANOVA test.

k Comparison between the groups used a Kruskal–Wallis test.

A *P*-value < .05 is considered statistically significant.

*,

** is considered that the data differ significantly from each other at the.05 level with a post hoc analysis.

Hypotension is defined as a blood pressure < 20% of baseline values. Bradycardia is defined as a heart rate < 60 beats per minute and/or a rapidly falling heart rate.

Table 3

Incidence of postoperative nausea and vomiting, and postoperative data.

	Fluid group (n = 55)	Ondansetron group (n = 49)	Control group (n = 52)	*P* value
Number of patients with				
Postoperative nausea and vomiting	16 (29.1)	9 (18.4)	13 (25)	.442
Postoperative nausea	16 (29.1)	9 (18.4)	13 (25)	.442
Postoperative vomiting	11 (20)	5 (10.2)	7 (13.5)	.353
Number of patients requiring				.028
Conservative treatment	0 (0)	2 (22.2)	5 (38.5)	
Pharmacological treatment	16 (100)	7 (77.8)	8 (61.5)	
Number of pharmacological treatments				.340
One antiemetic dose	15 (98.8)	5 (71.4)	7 (87.5.8)	
Pharmacological combination therapy	1 (6.3)	2 (28.6)	1 (12.5)	
Antiemetic drugs:				
Metoclopramide	14 (87.5)	7 (77.8)	8 (61.5)	.261
Domperidone	3 (18.8)	2 (22.2)	1 (7.7)	.599
Postoperative pain score	3 [0, 7]	4 [2, 8]	3 [2, 7.5]	.650
Postoperative morphine requirement (mg)	3 [0, 6]	3 [0–9]	3 [0, 8]	.560
Adverse events:				
Dizziness	1 (1.8)*	8 (16.3)*	4 (7.7)	.028
Headache	1 (1.8)	1 (2)	1 (1.9)	.997
Fever	4 (7.3)	4 (8.2)	6 (11.5)	.721
Desaturation (SpO_2 < 92%)	0 (0)	2 (4.1)	0 (0)	.109
Length of hospital stay (days)	2 [1, 2]	2 [1, 3]	2 [1.25, 3]	.080

Data are presented as number (percentage) or median [IQR].

Comparisons between the groups used Chi-squared or Kruskal–Wallis test.

A *P*-value < 0.05 is considered statistically significant.

* is considered that the data differ significantly from each other at the 0.05 level.

$SpO_{2\,=}$ pulse oxygen saturation.

Table 4

Subgroup analysis of incidence of postoperative nausea and vomiting based on age.

			PONV		PON		POV	
Ages	**Group**	**n**	**n(%)**	***P* value**	**n(%)**	***P* value**	**n(%)**	***P* value**
< 50 years	Fluid group	26	10 (38.5%)*	.008	10 (38.5%)*	.008	6 (23.1%)	.076
	Ondansetron group	20	0*,**		0*,**		0	
	Control group	20	6 (30.0%)**		6 (30.0%)**		3 (15.0%)	
> 50 years	Fluid group	29	6 (20.7%)	.601	6 (20.7%)	.601	5 (17.2%)	.838
	Ondansetron group	29	9 (31.0%)		9 (31.0%)		5 (17.2%)	
	Control group	32	7 (21.9%)		7 (21.9%)		4 (12.5%)	

Data are presented as number (percentage).

Comparisons between the groups used Chi-squared test. post hoc analysis used Bonferroni method. A *P* value < .050 is considered statistically significant.

*,

** is considered that the data differ significantly from each other at the.05 level with a post hoc analysis.

PONV = postoperative nausea and vomiting, PON = postoperative nausea, POV = postoperative vomiting.

antiemetic prophylaxis for PONV whilst adequate hydration is an effective strategy for reducing the risk of PONV.[1,7,18] However, the present study found that there was no statistical difference in overall incidences of PONV in LC patients receiving preoperative intravenous fluid loading (29.1%), intraoperative ondansetron (18.4%), and neither fluid nor ondansetron (25%).

The incidence of PONV in the control group was consistent with the levels reported by numerous studies, which ranged widely from 25% to 50% for laparoscopic cholecystectomies.[8,20,21] In our study, PONV occurred less frequently in patients receiving intraoperative ondansetron compared to those in the control and fluid groups (18% vs. 25% and 29.1%, respectively), but the difference was not statistically significant. Even though our study did not show a benefit of ondansetron in terms of overall PONV incidence, the subgroup analysis revealed that ondansetron was effective in preventing nausea and vomiting after surgery in patients under the age of 50. PONV and PON incidences in patients under 50 years in the ondansetron group (0%) had significantly lower than those in the control (30%) and fluid groups (38.5%). This 30% decrease in PONV/PON incidence resulting from the use of the ondansetron prophylaxis was noticeably similar to the reductions reported by other studies (21–40%, relative to placebos).[8,22]

A previous study also indicated that, compared with a placebo, the prophylactic administration of ondansetron was significantly effective in reducing both the number of episodes of emesis as well as the need for additional postoperative antiemetics for laparoscopic cholecystectomies.[8] Unfortunately, our study could not demonstrate any significant difference between the ondansetron and control groups in overall POV incidences (10.2% vs. 13.5%) and age-subgroup analysis (0% vs. 15%). According to our results, patients under the age of 50 got a benefit of ondansetron for decreasing PON. Whereas, patients aged 50 and over did not benefit from ondansetron for both PON and POV prophylaxis. To ascertain this result, more ondansetron research regarding PONV prophylaxis in patients under 50 may be necessary.

In this study, patients in the fluid group received a larger amount of fluid inside the operating theater than those in the ondansetron group and the control group significantly. An additional volume of approximately 500 mL of intravenous fluid administration was in accordance with the study protocol, which gave Ringer's lactate solution (10 mL/kg) for 15 minutes before the commencement of their operation. Surprisingly, our results did not show any reduction in PONV as a result of the preoperative intravenous fluid loading for the LC patients. These results are similar to those of several other studies, which were unable to show a significant difference between preoperative intravenous fluid loading and a placebo during the early postoperative period.[23–25] Instead, this study showed that the administration of the fluid had a tendency to unanticipatedly increase the incidences of PON and POV, relative to the control group. Subgroup analysis revealed that preoperative intravenous fluid loading significantly increased the incidence of PON for patients under 50 years of age when compared to the ondansetron group ($P < .050$). However, this effect was not demonstrated in patients 50 years old and older.

Additionally, the current study found that patients in the fluid group required significantly more pharmacological treatment for PONV than patients in the other two groups ($P = .028$). This suggests that the severity of PONV in the fluid group was greater than in the control and ondansetron groups. The data in this and other studies indicate that the effects of preoperative fluids on PONV are inconsistent: some studies have demonstrated the benefits of preoperative fluid administration,[12–17] whereas others have not shown these benefits.[14,26]

Turning to postoperative complications, dizziness was the only symptom that demonstrated a significant difference. The typical side effects of ondansetron are headache, dizziness, and arrhythmia. Therefore, the relatively high incidence of dizziness in the ondansetron group may have been a side effect of the ondansetron. This study manifested a similar incidence of dizziness to other studies in patients receiving ondansetron.[8,20,27] The length of hospital stay was 2 days in all three groups. Traditionally, patients undergoing LC in our hospital usually stay overnight after surgery for an academic purpose; our hospital context and facility may be different from other hospitals that send patients home the same day.

4.1. Limitation

This study has some limitations. Firstly, even though our study attempted to control both surgical and anesthetic factors, there were some variations, such as the duration of preoperative fasting, type of antibiotics, and nasogastric tube insertions. These factors may have caused some patients to either demonstrate or not experience PONV. Secondly, our study focused on a high-risk surgical procedure for PONV, LC; thus, participants in this study have at least one surgical risk factor for PONV. There may be several risk factors in addition to the surgery type, such as female gender, nonsmokers, history of PONV/motion sickness, and opioid use. About 70% of our participants were female, and this study used fentanyl and morphine for analgesia; these risk factors increase the incidence of PONV. Regarding the 4th consensus guidelines for the management of PONV, 1-2 risk factors need multimodal prophylaxis with two antiemetic agents for the prophylactic purpose.[1] Therefore, the current study protocol may be insufficient to effectively prevent PONV. However, the study protocol in this study may raise awareness of using PONV prophylaxis in our hospital, especially in high-risk surgical procedures. Lastly, our study examined only the incidence of early PONV. Additional data on late PONV, such as postoperative day 2 and post-discharge nausea and vomiting, may reveal greater effects for preoperative intravenous fluid loading and ondansetron.

5. Conclusions

Neither preoperative intravenous fluid loading nor ondansetron administration affected the incidence of early PONV in patients aged 50 and older undergoing LC, relative to patients who did not receive either intervention. Ondansetron was beneficial for PON prophylaxis in patients under the age of 50, whereas preoperative intravenous fluid loading was considered a risk factor for PON in this population. The postoperative morphine usage and the incidence of dizziness after surgery in the ondansetron group were significantly greater than those in the two other groups.

Acknowledgments

We thank all concerned staff at the Department of Surgery and the Department of Anesthesiology, Buddhachinaraj Hospital, for providing research support and expertise. We also thank Miss Chayanan Thanakiattiwibun for her assistance with the statistical analyses, manuscript preparation, and submission.

Authors contributions

Conceptualization: Mingkwan Wongyingsinn, Sirirat Charoensawan.
Data curation: Pechprapa Peanpanich.
Formal analysis: Mingkwan Wongyingsinn, Pechprapa Peanpanich.
Funding acquisition: Mingkwan Wongyingsinn.
Investigation: Mingkwan Wongyingsinn, Sirirat Charoensawan.
Methodology: Mingkwan Wongyingsinn, Pechprapa Peanpanich.

Project administration: Pechprapa Peanpanich.
Supervision: Mingkwan Wongyingsinn.
Validation: Mingkwan Wongyingsinn.
Visualization: Mingkwan Wongyingsinn.
Writing—original draft: Pechprapa Peanpanich.
Writing—review & editing: Mingkwan Wongyingsinn.

References

[1] Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2020;131:411–48.
[2] Chandrakantan A, Glass PS. Multimodal therapies for postoperative nausea and vomiting, and pain. Br J Anaesth. 2011;107:i27–40.
[3]Pierre S, Whelan R. Nausea and vomiting after surgery. Continuing education in anaesthesia. Crit Care Pain. 2013;13:28–32.
[4] Apfel CC, Korttila K, Abdalla M, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med. 2004;350:2441–51.
[5] Gan TJ. Postoperative nausea and vomiting – can it be eliminated? JAMA. 2002;287:1233–6.
[6] Thune A, Appelgren L, Haglind E. Prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. A prospective randomized study of metoclopramide and transdermal hyoscine. Eur J Surg. 1995;161:265–8.
[7] Nathan N. Management of postoperative nausea and vomiting: the 4th consensus guidelines. Anesth Analg. 2020;131:410.
[8] Liberman MA, Howe S, Lane M. Ondansetron versus placebo for prophylaxis of nausea and vomiting in patients undergoing ambulatory laparoscopic cholecystectomy. Am J Surg. 2000;179:60–2.
[9] McCracken G, Houston P, Lefebvre G. Society of obstetricians and gynecologists of Canada. Guideline for the management of postoperative nausea and vomiting. J Obstet Gynaecol Can. 2008;30:600–7, 608.
[10] Chandrakala R, Vijayashankara CN, Kumar KK, et al. Ondansetron induced fatal ventricular tachycardia. Indian J Pharmacol. 2008;40:186–7.
[11] Mehra KK, Gogtay NJ, Ainchwar R, et al. Hypersensitivity to intravenous ondansetron: a case report. J Med Case Re. 2008;2:274.
[12] Yavuz MS, Kazancı D, Turan S, et al. Investigation of the effects of preoperative hydration on the postoperative nausea and vomiting. Biomed Res Int. 2014;2014:302747.
[13] Elgueta MF, Echevarría GC, De la Fuente N, et al. Effect of intravenous fluid therapy on postoperative vomiting in children undergoing tonsillectomy. Br J Anaesth. 2013;110:607–14.
[14] Apfel CC, Meyer A, Orhan-Sungur M, et al. Supplemental intravenous crystalloids for the prevention of postoperative nausea and vomiting: quantitative review. Br J Anaesth. 2012;108:893–902.
[15] Lambert KG, Wakim JH, Lambert NE. Preoperative fluid bolus and reduction of postoperative nausea and vomiting in patients undergoing laparoscopic gynecologic surgery. AANA J. 2009;77:110–4.
[16] Turkistani A, Abdullah K, Manaa E, et al. Effect of fluid preloading on postoperative nausea and vomiting following laparoscopic cholecystectomy. Saudi J Anaesth. 2009;3:48–52.
[17] Maharaj CH, Kallam SR, Malik A, et al. Preoperative intravenous fluid therapy decreases postoperative nausea and pain in high risk patients. Anesth Analg. 2005;100:675–82.
[18] Hooper VD. SAMBA consensus guidelines for the management of postoperative nausea and vomiting: an executive summary for perianesthesia nurses. J Perianesth Nurs. 2015;30:377–82.
[19] Moghadamyeghaneh Z, Badami A, Masi A, et al. Unplanned readmission after outpatient laparoscopic cholecystectomy. HPB (Oxford). 2020;22:702–9.
[20] Erhan Y, Erhan E, Aydede H, et al. Ondansetron, granisetron, and dexamethasone compared for the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: a randomized placebo-controlled study. Surg Endosc. 2008;22:1487–92.
[21] Bisgaard T, Klarskov B, Kehlet H, et al. Preoperative dexamethasone improves surgical outcome after laparoscopic cholecystectomy: a randomized double-blind placebo-controlled trial. Ann Surg. 2003;238:651–60.
[22] Sridharan K, Sivaramakrishnan G. Drugs for preventing post-operative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: network meta-analysis of randomized clinical trials and trial sequential analysis. Int J Surg. 2019;69:1–12.
[23] Ali SZ, Taguchi A, Holtmann B, Kurz A. Effect of supplemental pre-operative fluid on postoperative nausea and vomiting. Anaesthesia. 2003;58:780–4.
[24] Spencer EM. Intravenous fluids in minor gynaecological surgery. Their effect on postoperative morbidity. Anaesthesia. 1988;43:1050–1.
[25] Keane PW, Murray PF. Intravenous fluids in minor surgery. Their effect on recovery from anaesthesia. Anaesthesia. 1986;41:635–7.
[26] McCaul C, Moran C, O'Cronin D, et al. Intravenous fluid loading with or without supplementary dextrose does not prevent nausea, vomiting and pain after laparoscopy. Can J Anaesth. 2003;50:440–4.
[27] Moon YE, Joo J, Kim JE, et al. Anti-emetic effect of ondansetron and palonosetron in thyroidectomy: a prospective, randomized, double-blind study. Br J Anaesth. 2012;108:417–22.