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CLINICAL TRIAL REPORT

Effects of Different Timing of Administration of Azasetron on the Prevention of Postoperative Nausea and Vomiting After Gynecological Laparoscopic Surgery: A Single Center, Double-Blind Randomized Controlled Trial

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Purpose: Postoperative nausea and vomiting (PONV) is a common complication in gynecological laparoscopic surgery. Azasetron is a commonly used injectable antiemetic for PONV prevention in clinical practice. However, the impact of its administration method, particularly the timing of administration, on PONV remains ambiguous. The objective of this study was to evaluate the impact of various administration regimens of azasetron on its antiemetic efficacy in patients undergoing laparoscopic gynecological surgery.

Methods: In this prospective study, 129 elective laparoscopic gynecological surgery patients were randomized 1:1:1 to three groups. Group A received azasetron 10 mg intravenously before anesthesia induction. Group B received azasetron 5 mg intravenously before induction and an additional 5 mg before the end of surgery. Group C received azasetron 10 mg intravenously before the end of surgery. The primary outcome was 24-hour PONV incidence. Secondary outcomes included PONV severity (0–2 and 2–24 hours), rescue antiemetic use within 24 hours, PACU and hospital stay lengths, and adverse events.

Results: There were no significant differences in the incidence and severity of PONV among Groups A, B, and C during the 24-hour follow-up period. The incidence of PONV 24 hours following surgery were 30.2%, 37.2%, and 30.2% (P = 0.728) in Groups A, B, and C, respectively. The incidence of postoperative adverse events was equivalent in both three groups. Group B demonstrated the highest demand for rescue antiemetic medications (P = 0.021), and the length of stay in the Post-Anesthesia Care Unit (PACU) was significantly extended (P = 0.012).

Conclusion: No significant difference was observed in PONV prevention within 24 hours postoperatively when comparing intravenous administration of 10 mg azasetron before anesthesia induction versus before surgical conclusion in gynecological laparoscopic surgery. In the context of 10 mg dosage of azasetron, the split-dose regimen increases the 24-hour rescue antiemetic requirements.

Keywords: azasetron, postoperative nausea and vomiting, gynecological laparoscopic surgery, randomized controlled trial

Introduction

Postoperative nausea and vomiting (PONV) represent one of the most prevalent adverse events encountered in clinical practice, often resulting in distress for patients.[1] In patients undergoing general anesthesia, the overall incidence of PONV ranges from 20% to 30%. In certain high-risk populations, this incidence may reach as high as 80%,[2] while in patients undergoing gynecological laparoscopic surgery under general anesthesia, the incidence ranges from 54% to 92%.[3] PONV can lead to reduced postoperative activity, challenges in nutritional intake, delayed recovery, increased hospitalization costs, and, in severe cases, death due to aspiration.[4,5]

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Currently, pharmacological strategies for the prevention and treatment of PONV have yielded some results. One of the primary mechanisms of PONV is the activation of the 5-hydroxytryptamine type 3 (5-HT_3) receptor. Inhaled narcotics and opioids induce enterochromaffin cells to release serotonin, which then binds to the 5-HT_3 receptor on the afferent fibers of the vagus nerve. This stimulation activates the brainstem vomiting center, ultimately resulting in vomiting.[6] Selective 5-HT_3 receptor antagonists function as antiemetic agents by binding to the 5-HT_3 receptor on the afferent nerve fibers of the intestinal vagus nerve.[7] Due to their efficacy and low incidence of adverse effects,[8] PONV guidelines recommend selective 5-HT_3 receptor antagonists as the first-line agents for the prevention of PONV in high-risk patients.[9]

Azasetron, a first-generation selective 5-HT_3 receptor antagonist, exhibits a long half-life of 5.4 hours and high selectivity for the 5-HT_3 receptor.[10] Current research indicates that although azasetron is used off-label for preventing PONV, it effectively reduces nausea and vomiting through competitive antagonism of the 5-HT_3 receptor—the same mechanism underlying its use in chemotherapy-induced nausea and vomiting (CINV) prevention.[11] Azasetron has been widely adopted in clinical practice for the management of PONV.[12] It has been demonstrated that azasetron, at a dosage of 10 mg, is no less effective than ondansetron at 8 mg in preventing PONV following gynecological laparoscopic surgery. Azasetron exhibits superior efficacy in the 12–24 hours postoperative period.[13] Meanwhile, azasetron for the prevention and treatment of PONV is not included in the fourth edition of the PONV consensus guidelines.[9] The prophylactic administration of azasetron before surgery to prevent PONV is modeled after its use in preventing CINV.[14] Additional clinical evidence is required to support the use of azasetron in the prevention of PONV. The administration method, particularly the timing, remains unclear.

Therefore, we conducted a randomized, double-blind, controlled trial to examine the effect of different administration methods on the prevention of PONV after gynecological laparoscopic surgery. We hypothesize that one of the three administration modes of azasetron will lead to a lower incidence of nausea and vomiting.

Methods

A prospective, single-center, randomized, double-blind, controlled trial, conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement, was performed from October 2023 to January 2025 at a public tertiary hospital. This study received approval from Ethics committee of Central Hospital of Dalian University of Technology (YN2023-104-01) on September 18, 2023. The research program was registered prior to patient enrollment, at the Chinese Clinical Trial Registry (ChiCTR2300076786, Principal investigator: Liping Han, Date of registration: October 18, 2023, https://www.chictr.org.cn/bin/project/edit?pid=208485). All participants provided written informed consent.

Participants

Eligible patients were aged 18 to 75 years, weighed no more than 60 kg, were classified as American Society of Anesthesiology (ASA) physical status I to III, and were scheduled for gynecologic laparoscopic surgery. The exclusion criteria included: (1) history of drug allergy to serotonin receptor antagonists; (2) Impaired liver and kidney function; (3) history of motion sickness or postoperative nausea and vomiting (PONV); (4) Patients with a history of smoking; (5) Patients with a history of gastrointestinal disease, vertigo, conditions increasing intracranial pressure, or recent chemotherapy for malignant tumors.

Randomization and Blinding

Patients were randomly assigned to Group A (intravenous infusion of 10 mg of azasetron [Yangtze River Pharmaceutical Group Co., Ltd, China] before anesthesia induction), Group B (5 mg of azasetron before induction and another 5 mg before the end of surgery), or Group C (intravenous infusion of 10 mg of azasetron before the end of surgery). An independent investigator generated a sequence of random numbers using Microsoft Excel 2016 and assigned them in a 1:1:1 ratio, sealing the numbers in sequentially numbered opaque envelopes. The opaque envelope containing the group assignments will be provided to the anesthesiologist responsible for intraoperative management when the patient enters the operating room. The anesthesiologist will administer azasetron according to the assigned dosing regimens for each group. Preoperatively, azasetron was constituted in normal saline to yield concentrations of 0.1 mg/mL (5 mg/50 mL) and 0.2 mg/mL (10 mg/50 mL). Both formulations appeared colorless and transparent. Group B received 5 mg azasetron (in 50 mL) before induction and another

5 mg dose (in 50 mL) before the end of surgery. Groups A and C received single 10 mg doses (in 50 mL). To maintain blinding, 50 mL normal saline alone was administered at scheduled time points when azasetron was not indicated. An independent researcher, uninvolved in the prior procedures, will evaluate the outcomes.

Procedures

None of the patients received pre-anesthetic medications, while all patients adhered to standardized anesthesia protocols. After the patient enters the operating room, routine monitoring commences, and baseline vital sign values are recorded. Open venous access is established, followed by the intravenous infusion of lactated Ringer's solution. Prior to the induction of anesthesia, all subjects were preoxygenated, and the depth of anesthesia was monitored using the bispectral index (BIS). Anesthesia was induced using 0.4 $mg \cdot kg^{-1}$ of ciprofol and 0.5 $\mu g \cdot kg^{-1}$ of sufentanil. During manual ventilation, the adjustable pressure-limiting (APL) valve pressure should not exceed 20–30 cm H_2O to prevent gastric insufflation. The intra-abdominal CO_2 pressure was maintained at 12 cm H_2O during the surgical procedure. Under the guidance of the BIS values, rocuronium at a dose of 0.6 $mg \cdot kg^{-1}$ was administered to facilitate tracheal intubation. Following induction, 5 mg of dexamethasone was administered intravenously. Intraoperative anesthesia was maintained through the intravenous administration of $5mg \cdot kg^{-1} \cdot h^{-1}$ propofol and 0.05–0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil using a target-controlled infusion pump, with the pumping speed adjusted according to the BIS values. Adjust the pump speed as necessary to maintain BIS values between 40 and 60. Ephedrine was administered according to the department's medical guidelines to maintain the mean arterial pressure within a range that does not decrease by more than 20%. At the conclusion of the surgery, all patients received neostigmine to reverse residual neuromuscular blockade, along with 10 mg of nalbuphine for prophylactic postoperative analgesia. In addition to sufentanil and remifentanil, no other opioid analgesics were employed in this study.

Outcomes

The primary outcome was the incidence of PONV within 24 hours after surgery. Secondary outcome measured encompassed severity of PONV, severity of nausea, frequency of vomiting, the need for rescue antiemetics within 24 hours, length of PACU stay, length of hospital stay, Incidence of postoperative adverse events (including thirst, constipation, dizziness, headache, abdominal discomfort).

Outcome Measures and Data Collection

The baseline characteristics for all subjects were recorded. Following postoperative assessment by the nurse anesthetist, subjects were transferred to the general ward when they achieved an Aldrete post-anesthesia recovery score of at least 9 points.[15] Concurrently, the duration of PACU stay was ascertained. The occurrence of nausea and vomiting was assessed using the simplified PONV impact scale (Myles et al)[16] at two distinct time points: 2 hours and 24 hours post-surgery. The simplified PONV impact scale has a maximum score of 6, with scores no less than 5 defined as clinically important PONV. Patient outcomes data were collected in accordance with a pre-established protocol. The severity of nausea was assessed utilizing the simplified PONV impact scale with four grades: Not at all, Sometimes, Often, and All the time. In assessing vomiting episodes, consecutive occurrences within a brief interval, such as those separated by only 5 minutes, should be considered a single episode. As a rescue antiemetic intervention, 10 mg of metoclopramide was administered intravenously upon the ward physician's request when the patient exhibited clinically important PONV or made a specific request. Surgical information, including length of PACU stay, length of hospital stay, was retrospectively obtained from the inpatient medical record system.

Statistical Analysis

Preliminary experimental results indicated that the incidence of postoperative nausea and vomiting across Groups A, B, and C was 60%, 40%, and 20%, respectively. With a two-sided alpha level of 0.05 and a power of 0.9, accounting for a 10% follow-up loss rate, the study included a total of 129 participants, with 43 allocated to each group.

Statistical analyses were conducted using SPSS Statistics version 25.0 (Inc., Chicago, Illinois, USA). Bilateral P values <0.05 were considered statistically significant. Categorical variables are presented as numbers (percentages

[%]) and analyzed using the Chi-square test or the Kruskal–Wallis test, as appropriate. Continuous variables are summarized using the mean (standard deviation [SD]) or median (interquartile range [IQR]). The Analysis of Variance (ANOVA) test was employed for normally distributed variables, while the Kruskal–Wallis test was utilized for non-normally distributed data. Post hoc comparisons were performed using the Bonferroni method or the Chi-square segmentation technique.

Results

A total of 150 patients undergoing gynecologic laparoscopy were screened between October 2023 and January 2025. Of these, 140 patients who met the inclusion criteria were randomly assigned to Groups A, B, and C. Six patients who requested patient-controlled intravenous analgesia (PCIA) or received rescue analgesia were excluded from the evaluation. Two patients converted from laparoscopic to open surgery and were subsequently excluded. Three patients were excluded due to postoperative requests for early discharge. Ultimately, 129 patients were included in the final analysis, as detailed in the CONSORT flow diagram (Figure 1). The analysis included 129 patients, each of whom underwent one of four types of surgery (P = 0.632). According to Apfel's PONV risk score, all participants were non-smoking women undergoing gynecologic laparoscopic surgery, with a calculated PONV risk of 61%.[2] The demographic characteristics of the three patient groups are presented in Table 1.

The three treatment groups were comparable regarding baseline characteristics, including age, height, weight, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, anesthesia duration, operative duration, and intraoperative ephedrine dosage.

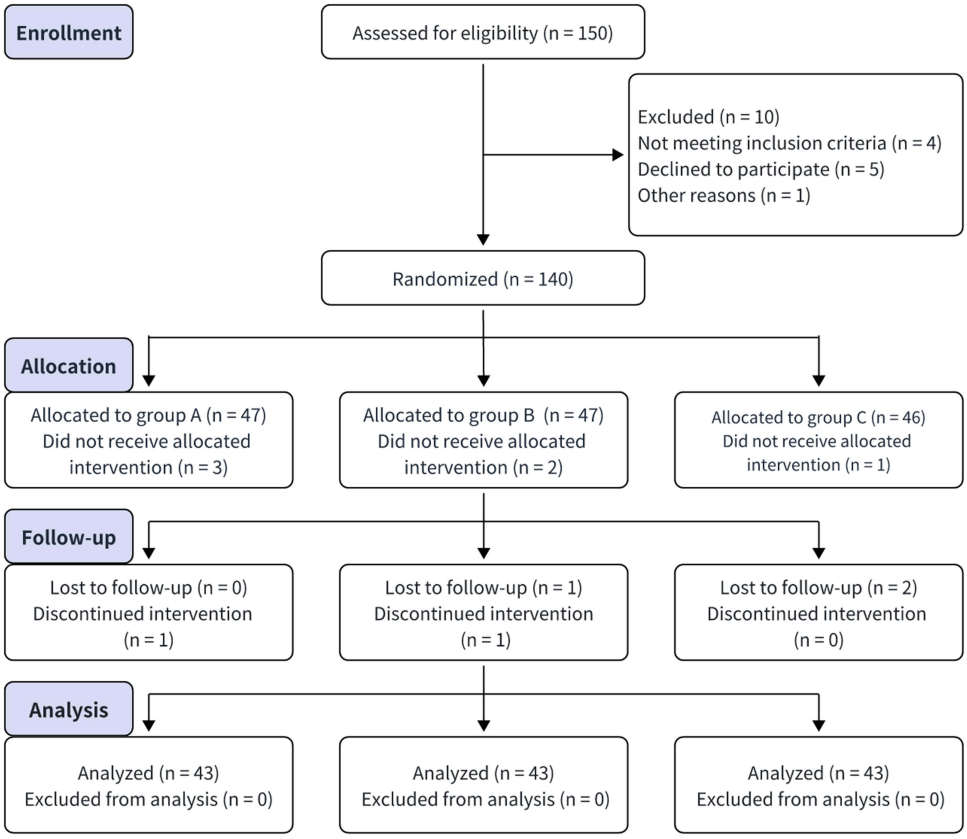

Figure 1 CONSORT (Consolidated Standards of Reporting Trials) flow diagram of the study.

Table 1 Demographic and Baseline Characteristics of Studied Groups

	Group A	Group B	Group C	P-value
Age(yr)	46.6 (11.4)	45.2 (10.9)	45.3 (9.4)	0.789
Height(cm)	161 (5.0)	161.6 (4.7)	161.7 (4.9)	0.814
Weight(kg)	59 (55–60)	59 (55–60)	57.5 (55–60)	0.813
BMI (kg/m2)	22 (1.7)	21.9 (1.6)	21.6 (2.2)	0.549
ASA Score				
1	23 (53.5%)	21 (48.8%)	22 (51.2%)	0.905
2	17 (39.5%)	19 (44.2%)	16 (37.2%)	
3	3 (7%)	3 (7%)	5 (11.6%)	
Surgical Procedure				
Hysterectomy	15 (34.9%)	16 (37.2%)	18 (41.9%)	0.632
Adnexectomy	3 (7%)	6 (14%)	6 (14%)	
Myoma Enucleation	14 (32.6%)	11 (25.6%)	14 (32.6%)	
Oophorocystectomy	11 (25.6%)	10 (23.3%)	5 (11.6%)	
Anaesthesia Time (min)	70 (55–85)	75 (65–100)	63 (55–85)	0.078
Surgical Time (min)	50 (40–67)	57 (40–70.0)	48 (37–70)	0.531
Length of PACU stay (min)	20.7 (8.2)	25 (7.9)*	19.8 (7.8)	0.012
Length of hospital stay (days)	7 (6–8)	7 (7–8)	7 (6–8)	0.087
Ephedrine (mg)	1.4 (3.9)	2.1 (6.1)	1.5 (4.6)	0.612

Notes: Variables are summarized by number of patients (%), means ± standard deviation, or medians (interquartile range), as appropriate. *The length of the PACU stay in Group B was significantly longer than that in Group C (P = 0.015). No significant differences were found between Group A and Group B (P = 0.065), or between Group A and Group C (P > 0.999).

Abbreviations: ASA, American Society of Anesthesiology; BMI, Body mass index; PACU, Post-Anesthesia Care Unit.

PONV-Related Outcomes

As shown in Table 2, the incidence of PONV at any time within 24 hours after surgery was 30.2% in Group A, 37.2% in Group B, and 30.2% in Group C. There were no significant differences among the three groups (P = 0.728). The requirement for

Table 2 Postoperative Nausea and Vomiting (PONV)-Related Outcomes

	Group A	Group B	Group C	P-value
PONV at any time	13 (30.2%)	16 (37.2%)	13 (30.2%)	0.728
Rescue antiemetics	1 (2.3%)	9 (20.9%)*	3 (7%)	0.021
Nausea, 0–2hr				
Not at all	37 (86%)	35 (81.4%)	37 (86%)	0.744
Sometimes	4 (9.3%)	3 (7%)	5 (11.6%)	
Often	2 (4.7%)	2 (4.7%)	1 (2.3%)	
All the time	0	3 (7%)	0	
Vomiting, 0–2hr				
0	41 (95.3%)	37 (86%)	41 (95.3%)	>0.999
1	1 (2.3%)	3 (7%)	2 (4.7%)	
2	0	2 (4.7%)	0	
≥3	1 (2.3%)	1 (2.3%)	0	
Nausea, 2–24hr				
Not at all	36 (83.7%)	31 (72.1%)	35 (81.4%)	0.255
Sometimes	7 (16.3%)	6 (14%)	6 (14%)	
Often	0	3 (7%)	2 (4.7%)	
All the time	0	3 (7%)	0	

(*Continued*)

Table 2 (Continued).

	Group A	Group B	Group C	P-value
Vomiting, 2–24hr				
0	37 (86%)	32 (74.4%)	28 (65.1%)	0.283
1	3 (7%)	6 (14%)	2 (4.7%)	
2	2 (4.7%)	2 (4.7%)	3 (7%)	
≥3	1 (2.3%)	3 (7%)	1 (2.3%)	
Simplified PONV impact scale score,0–2hr				
0	37 (86%)	35 (81.4%)	38 (88.4%)	0.709
1	0	0	1 (2.3%)	
2	5 (11.6%)	3 (7%)	2 (4.7%)	
3	0	2 (4.7%)	2 (4.7%)	
4	0	1 (2.3%)	0	
5	1 (2.3%)	2 (4.7%)	0	
Simplified PONV impact scale score, 32–24hr				
0	35 (81.4%)	30 (69.8%)	34 (79.1%)	0.273
1	2 (4.7%)	1 (2.3%)	1 (2.3%)	
2	3 (7%)	3 (7%)	5 (11.6%)	
3	2 (4.7%)	4 (9.3%)	1 (2.3%)	
4	1 (2.3%)	1 (2.3%)	0	
5	0	4 (9.3%)	2 (4.7%)	

Notes: Variables are summarized by number of patients (%). *The incidence of requiring rescue antiemetics in Group B was significantly higher compared to that in Group A (P = 0.015). No significant differences were found between Group B and Group C (P = 0.117), or between Group A and Group C (P = 0.616).

rescue antiemetics differed among groups: nine patients in Group B, two in Group C, and one in Group A needed intervention. Post hoc Bonferroni analysis revealed significantly higher rescue antiemetic requirements in Group B versus Group A (P = 0.015). This suggests that the split-dose treatment significantly increased the need for rescue antiemetics (P = 0.021). The severity of nausea was categorized, with the majority of patients in all groups reporting "Not at all" at 0–2 hours and 2–24 hours postoperatively. However, "Often", and "All the time" categories showed a higher incidence in Group B compared to Groups A and C (Figure 2a and b), though these differences were not statistically significant (P values of 0.744 and 0.255 for 0–2 hours and 2–24 hours, respectively). Vomiting episodes within the same time frames followed a similar pattern, with Group B showing a higher incidence of 1 or more episodes compared to Groups A and C (Figure 2c and d), still again, these differences were not statistically significant (P value of 0.999 for 0–2 hours and 0.283 for 2–24 hours). The Simplified PONV impact scale score at 0–2 hours and 2–24 hours postoperatively revealed a higher incidence of scores ≥1 in Group B compared to Groups A and C, with P values of 0.709 and 0.273, respectively, indicating no significant difference (Table 2).

Length of PACU and Hospital Stay

As shown in Table 1, the post-anesthesia care unit (PACU) time for Group B was 25 ± 7.9 minutes, indicating a statistically significant difference compared to the other two groups (P = 0.012). The Bonferroni method was employed for post hoc comparisons. The length of the PACU stay in Group B was significantly longer than that in Group C (P = 0.015). However, there was no significant difference in residence time between Group A and Group B (P = 0.065) or between Group A and Group C (P > 0.999). Furthermore, there was no significant difference in length of hospital stay among the three groups (P = 0.087).

Adverse Events

In the analysis of postoperative adverse events within the first 24 hours, the incidence of thirst, constipation, dizziness, headache, and abdominal discomfort was compared across Groups A, B, and C. The results indicated no significant differences in the occurrence of these events among the groups (Table 3).

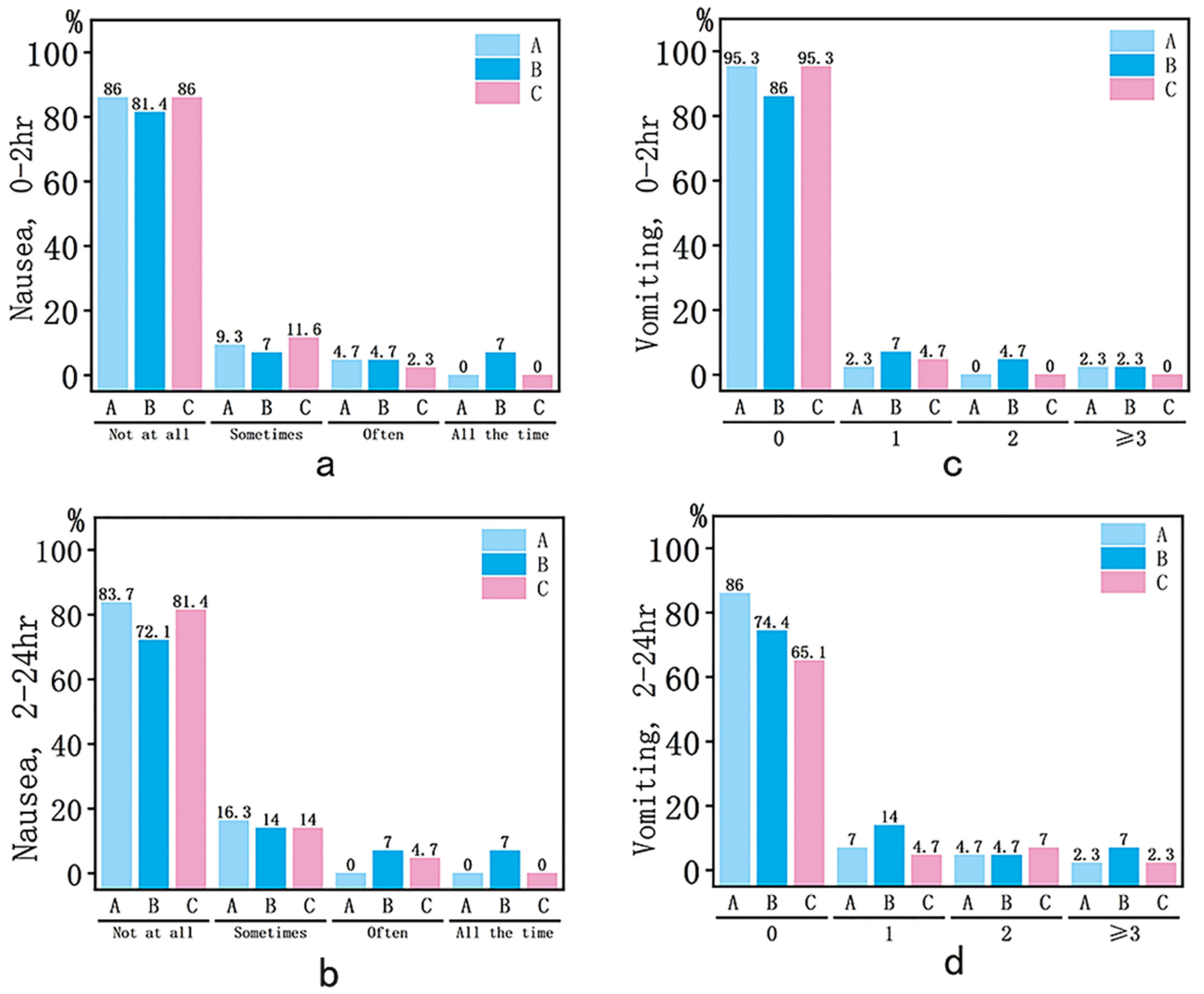

Figure 2 Percentage of patients by nausea severity and vomiting frequency in Groups A, B, and C within 0–2 and 2–24 hours postoperatively. (**a**) Percentage of patients by nausea severity 0–2 hours postoperatively; (**b**) Percentage of patients by nausea severity 2–24 hours postoperatively; (**c**) Percentage of patients by vomiting frequency 0–2 hours postoperatively; (**d**) Percentage of patients by vomiting frequency 2–24 hours postoperatively.

Discussion

This study evaluated the effects of intravenous administration of a 10 mg background dose of azasetron using three different methods on the control of PONV within 24 hours following gynecological laparoscopic surgery. Compared with the preoperative PONV risk of 61%, the postoperative incidence of nausea and vomiting was substantially reduced in Groups A, B, and C (30.2%, 37.2%, and 30.2%, respectively). No significant differences were observed in the overall

Table 3 Incidence of Adverse Events

	Group A	Group B	Group C	P-value
Thirst	3 (7%)	4 (9.3%)	3 (7%)	>0.999
Constipation	5 (11.6%)	3 (7%)	1 (2.3%)	0.295
Dizziness	6 (14%)	6 (14%)	7 (16.3%)	>0.999
Headache	2 (4.7%)	3 (7%)	2 (4.7%)	>0.999
Abdominal Discomfort	2 (4.7%)	6 (14%)	3 (7%)	0.381

Notes: Variables are summarized by number of patients (%).

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incidence of PONV among the groups. The severity of nausea and the frequency of vomiting were no significant difference among the three groups during the 0–2 hours and 2–24 hours postoperative periods. Concurrent with the evaluation of PONV severity, five patients in Group B exhibited clinically significant PONV.[16] However, this difference did not achieve statistical significance (P = 0.065). Additionally, the split-dose regimen resulted in a higher demand for rescue antiemetics and correlated with extended length of the PACU stay.

Ondansetron, tropisetron, ramosetron, and palonosetron etc., which are 5-HT_3 receptor antagonists, are considered safe and effective for preventing PONV after general anesthesia.[17–20] Compared to other classes of antiemetic medications, 5-HT_3 antagonists exhibit fewer side effects, including sedation, dry mouth, headache, dizziness, and blurred vision.[4,21,22] Azasetron, a 5-HT_3 receptor antagonist developed and marketed in Japan,[23,24] enjoys widespread use in Asia for the clinical management of PONV.[12,13,25] This medication has been a staple in our medical center for years. Nonetheless, it is not included in the 2020 guidelines for PONV prevention.[9] Moreover, the timing of administration for various types of 5-HT_3 antagonists in the prevention of PONV is not uniform.[26–28] Consequently, further research into the dosing regimen of azasetron for PONV prophylaxis is warranted.

The choice of a 10 mg total dose of azasetron in this study was informed by the standard single dose employed for the prevention of CINV.[29] In the study by Yun et al,[13] the administration of 10 mg of azasetron five minutes prior to the conclusion of surgery PONV after gynecological laparoscopic procedures, resulting in an overall PONV incidence of 49%. This incidence is higher than the 30.2% observed in Group C. In contrast to the current study, Yun et al utilized opioids for postoperative pain management and azasetron as the sole antiemetic, omitting the addition of dexamethasone. They observed an average anesthesia duration of 90.6 ± 26 minutes. The observed increase in PONV incidence can be attributed to the synergistic effects of these factors when considered in concert. In alignment with Tang et al's study,[17] this research implemented three distinct dosing regimens. However, we diverged by not including a placebo group, as it would be unethical to withhold prophylactic treatment from high-risk individuals for the prevention or mitigation of PONV. Tang et al suggest that administering ondansetron at the end of surgery, as opposed to prior to anesthesia induction, could potentially enhance patient outcomes. The preoperative administration of ondansetron is grounded in the hypothesis of the preemptive approach, which posits that blocking the receptor centers in advance of a vomiting stimulus can enhance therapeutic efficacy, akin to the principles of preemptive analgesia.[30] However, considering the short elimination half-life (2.8 ± 0.6 hours) of ondansetron,[31] administration at the conclusion of surgery may offer a superior therapeutic option. Our results demonstrated that the various administration patterns of azasetron in Groups A, B, and C did not result in significant differences in the incidence of PONV prevention following gynecological laparoscopic surgery that lasted one hour or so (the duration of anesthesia for Groups A, B, and C was 70 (55–85) minutes, 75 (65–100) minutes, and 63 (55–85) minutes, respectively). The effect of the timing of administration on the effectiveness of antiemetic treatment appears to be dependent on the specific medication used. On one hand, the elimination half-life of azasetron, approximately 5.4 hours,[10] significantly exceeded the duration of surgery for the patients in this study, thereby minimizing the half-life's influence on PONV prevention. On the other hand, Shah et al have documented that dolasetron is metabolized into its active form, hydrogen dolasetron, which possesses an elimination half-life of approximately 7–9 hours and exhibits antagonistic potency 100-fold that of the parent compound.[32] This suggests that the absence of differences in dosing timing for the prevention of PONV may be attributable to the presence of similar metabolites of azasetron, should they exist. Unfortunately, there is a dearth of research concerning the pharmacokinetics of azasetron. Additionally, a study by Endo et al evaluating the antiemetic effects based on 5-HT_3 receptor occupancy found that azasetron exhibited the highest receptor occupancy among various 5-HT_3 antagonists.[14] In the initial hours following intravenous administration, azasetron demonstrated a receptor occupancy rate of nearly 100% and an overall occupancy rate exceeding 85% within a 24-hour period. Following intravenous administration, azasetron achieved nearly 100% receptor occupancy in the initial hours and maintained an overall occupancy rate exceeding 85% within 24 hours. In contrast, ondansetron exhibited the lowest receptor occupancy, with levels dropping below 40% at 12 hours and to 18.5% by 24 hours. Thus, during the 24-hour observation period, no significant differences were observed in the therapeutic effects of the different administration methods for preventing PONV across Groups A, B, and C.

In this study, the administration of regular dosage and the exclusion of patients with significant body weight did not augment the financial burden on patients nor influence the basic effectiveness. Split-dose administration is commonly

employed to enhance effectiveness and minimize complications or adverse reactions while achieving therapeutic or preventive effects that are at least equivalent to those obtained with a single dose.[33,34] This study employs a split-dose administration strategy consisting of preoperative preloading combined with intraoperative top-up supplementation. This approach may optimize PONV prophylaxis by maintaining stable therapeutic plasma concentrations throughout the intraoperative and early postoperative periods. However, this hypothesis has not been systematically validated in comparable studies, while existing research remains limited to horizontal comparisons of single-dose administration timing.[35] Conversely, the split-dose regimen in Group B significantly increased postoperative rescue antiemetic requirements (20.9%, P = 0.021) and prolonged PACU stays (P = 0.012). Although the results were not statistically significant, as shown in Figure 2, Group B displayed a higher frequency of one or more episodes when compared to Groups A and C. Specifically, the categories "Often", and "All the time" indicated a greater prevalence in Group B than in Groups A and C. Caution is warranted when interpreting these findings, as they suggest that a 5 mg dose of azasetron, which remains within the recommended dosage for mammals,[23] administered prior to induction may not be adequate to prevent PONV in all patients. Additionally, the same dose added before the conclusion of surgery may fail to achieve the optimal effective concentration. The risk factors for PONV were comparable across the three groups, with baseline characteristics showing no significant differences. Thus, it was justified to attribute variations in PACU stay duration to the distinct dosing regimens employed. The prolonged PACU stay in Group B may be associated with increased rescue antiemetic requirements, as vomiting directly prolongs patient recovery time in this setting. Future research should aim to establish the optimal dosing regimen, timing, and route of azasetron for the PONV, as these aspects have yet to be fully determined.

This randomized controlled trial presents at least three limitations. Firstly, it is an exploratory study investigating the prophylactic use of azasetron for the prevention of PONV, necessitating a larger clinical trial in the future. Secondly, due to ethical considerations, a placebo group was not established, indicating that the effectiveness of azasetron in preventing PONV requires further verification. Finally, this study did not comprehensively account for all potential confounding factors that may influence the incidence of postoperative nausea and vomiting, such as intraoperative opioid consumption. Meanwhile, by excluding patients >60 kg and those with a history of smoking, PONV, or motion sickness, the resulting study population consisted of a lower-risk cohort that may not fully represent typical clinical cases. Further studies in higher-risk populations are warranted to validate these results.

Conclusion

In conclusion, no significant difference was observed in the efficacy of intravenous 10 mg azasetron for preventing PONV within 24 hours postoperatively when administered before anesthesia induction versus prior to surgical completion in gynecological laparoscopic surgery. No significant differences were observed in PONV incidence, severity, or length of PACU stay between the two treatment groups. Additionally, compared with the calculated PONV risk, an intravenous infusion of 10 mg azasetron reduced the incidence of PONV within 24 hours post-surgery. The split-dose regimen was associated with higher rescue antiemetic use and longer PACU stay and therefore appears less favorable; larger studies are needed before making firm recommendations.

Abbreviations

PONV, Postoperative nausea and vomiting; PACU, Post-Anesthesia Care Unit; 5-HT3, 5-hydroxytryptamine type 3; CINV, chemotherapy-induced nausea and vomiting; CONSORT, Consolidated Standards of Reporting Trials; ASA, American Society of Anesthesiology; BIS, bispectral index; APL, adjustable pressure-limiting; SD, standard deviation; IQR, interquartile range; ANOVA, Analysis of Variance; PCIA, patient-controlled intravenous analgesia; BMI, Body mass index.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study is in line with the principles of the Declaration of Helsinki. The study received approval from Ethics committee of Central Hospital of Dalian University of Technology (YN2023-104-01) on September 18, 2023. The

research program was registered prior to patient enrollment, at the Chinese Clinical Trial Registry (ChiCTR2300076786, Principal investigator: Liping Han, Date of registration: October 18, 2023, https://www.chictr.org.cn/bin/project/edit?pid=208485). All participants provided written informed consent.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report that they have no conflict of interests.

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