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Original study

Comparison of the effects of Aprepitant and Granisetron in preventing postoperative nausea and vomiting (PONV) in patients undergoing Laparoscopic Cholecystectomy: A double-blind, randomized, controlled study

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Abstract

Background: **Postoperative nausea and vomiting (PONV) is one of the most common findings in the first 24 hours after surgery, occurring in 30% of all patients and up to 80% of high-risk patients. We compared aprepitant (a neurokinin-1 receptor antagonist) and granisetron in preventing PONV in patients who underwent laparoscopic cholecystectomy (LC).**
Methods: **Sixty-one patients (aged 18-90) and the American Society of Anesthesiologists (ASA) I-II class who underwent LC under general anesthesia were enrolled in the study. Our study aimed to compare the incidence of PONV between 0-6, 6-12, and 6-24 hours postoperatively and the need for additional antiemetic requirements primarily and, secondly, detecting VAS scores and additional analgesic requirements for aprepitant and granisetron. Results: Our study observed similar PONV changes in both groups at 0-6 hours. A significantly lower VDS was observed in group A at 30-60 minutes compared to group G (p=0.10). There was no significant difference between groups at other intervals until the 120th minute. Between 6 and 12 hours, Group A had a lower VDS (Verbal Descriptive Scale) than Group G, but there was no statistically significant difference (P>0.05). There was no significant difference between the groups regarding VAS scores, additional analgesic requirements, and adverse effects on patients (p>0.05).**
Conclusion: **We observed that aprepitant may be more effective than granisetron in preventing PONV and can be used safely in patients undergoing LC.**

Keywords: **Aprepitant, granisetron, postoperative nausea and vomiting, laparoscopic cholecystectomy.**

Introduction

Postoperative nausea and vomiting (PONV) is one of the most common findings in the first 24 hours after surgery, occurring in 30% of all patients and up to 80% of high-risk patients. Risk factors in PONV are multifactorial and involve female gender, age less than 50 years, nonsmoking status, motion sickness or history of PONV, anxiety, obesity, nitrous oxide, and inhalation anesthetic agents, opioids, reversal of neuromuscular blockade, pain, type, and longer duration and location of surgery can affect the incidence of PONV[1-3].

PONV may cause discomfort in the patient, especially discharge after day surgery delay, dehydration in patients who vomit excessively, electrolyte disturbance, lung aspiration, and may even cause the surgical wound to open. The frequency of PONV is higher in laparoscopic cholecystectomy performed under general anesthesia[3-5].

Despite introducing new anesthetic techniques and many antiemetics agents (Histamine H2 receptor

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antagonists, dopamine receptor antagonists, anticholinergic agents, serotonin 5-HT3 receptor antagonists, and corticosteroids) into clinical use has not been entirely resolved, PONV continues to be a significant problem[6,7].

Granisetron is highly selective and a potent serotonin 5-HT3 receptor antagonist with a halflife of 4-6 hours used for many years to prevent PONV[1]. In recent years, as a new class of drugs, aprepitant, known as a highly selective brain-penetrating non-peptide neurokinin1 (NK1) receptor antagonist, has been used in the clinic against peripheral and central emetic stimuli. Aprepitant has a long half-life (9-13 hours), especially against PONV caused by chemotherapy and after surgery used in combination with other antiemetics[4-8].

Herein, we compared aprepitant and granisetron in preventing PONV in patients who underwent LC patients under general anesthesia.

Materials and Methods

Our study was organized and conducted by the ethical principles of the Declaration of Helsinki. This randomized, double-blind, controlled clinical study was conducted as a single center between November 2022 and January 2023. Our study was approved by the Başkent University Medical Faculty Ethics Committee (approval number: KA22/252, 2022) and registered with Clinicaltrials.gov (NCT05632224). Sixty-one patients (aged 18-90) and the American Society of Anesthesiologists (ASA) I-II class who underwent LC under general anesthesia were enrolled in the study. Our study targeted to compare the incidence of PONV between 0-6, 6-12, and 6-24 hours postoperatively and the need for additional antiemetic requirements primarily and, secondly, detecting VAS scores and additional analgesic requirements for aprepitant and granisetron. Exclusion criteria were ASA III patients, allergy to the drugs used in the trial (Granisetron, aprepitant, propofol, fentanyl, rocuronium), had contraindications for the studied medications, history of motion sickness or vertigo, psychiatric diseases, previous postoperative PONV, pregnant, menstruating women, lactating, use of an antiemetic agent within 24 hours before surgery. Patients who refused to participate in this trial were excluded, too. The smoking status was recorded for each patient. The patient-controlled analgesia device was not prepared for the patients in the postoperative period.

Written and verbal informed consent were obtained from all patients before the operation, and they were not informed about which group they belonged to. The Consolidated Reporting Trials (CONSORT) flow plan was used for patient enrollments (Figure 1), and this study's allocation and reporting were monitored with the CONSORT reporting protocol. The same team of anesthesiologists and surgeons performed all LC procedures. Different anesthesiologists performed the data collection and treating roles in this study.

Randomization was performed in two groups of 61 patients using a computer-generated random number table. Patients in the group aprepitant (n=31) were administered orally 40 mg 1 hour before the induction of anesthesia by the general surgery nurse, and the group granisetron (n=30) received 3 mg intravenous (IV) 10 min before extubation.

All patients were preoperatively examined in the anesthesia outpatient and general surgery departments. Preoperative blood and imaging tests were routinely performed at our hospital before surgery. APFEL score for PONV was calculated for all patients. This score includes gender (female 1 point and male 0 points), history of smoking, previous PONV history, motion sickness, and usage of postoperative opioid drugs.

All patients were taken to the operating room with premedication (with IV midazolam 1-2 mg) and then monitored with standard ASA monitoring: 5-lead electrocardiography, heart rate (HR), peripheral oxygen saturation (SpO2), non-invasive blood pressure as mean arterial pressure (MAP), end-tidal carbon dioxide (EtCO2). Anesthesia induction was done with 1 mg/kg of lidocaine, 2 mg/kg of propofol, 1µg/kg of fentanyl, and 0.6 mg/kg of rocuronium. After about three minutes of preoxygenation, endotracheal intubation with direct laryngoscopy was performed. The anesthesia was maintained in both groups with 0.01-0.2 µg/kg/min. IV remifentanil infusion and 2-3% sevoflurane in a 50%/50% air-oxygen mixture. The orogastric tube was inserted in all patients and extracted at the end of the surgical procedure. Ventilator settings were a fraction of inspired oxygen (FiO2) 40%, tidal volume 4-6 mL/kg, respiratory rate 12-14/min, positive end-expiratory pressure (PEEP) 4-6 mmHg. Both groups received 100 mg of tramadol as an analgesic drug. The end of the surgery was defined as the time the surgeon completed dressings. Immediately after, all anesthetic drugs were discontinued, the patient was ventilated with 80% oxygen, and neuromuscular blockade was antagonistic with 2 mg/kg sugammadex. Patients were extubated after a train of four (TOF) rate>0.9 was achieved, and rhythmic respiratory volume was observed during spontaneous breathing. After complete recovery, patients were transferred to the postanesthesia care unit (PACU) and followed

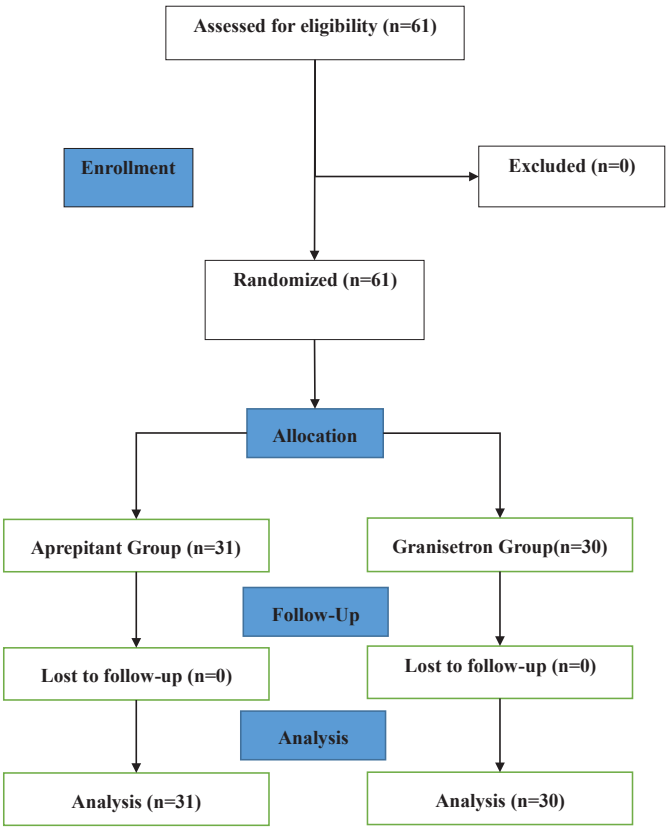

Fig. 1 — CONSORT flow Diagram.

until they achieved the modified Aldrete score of ≥9.

Surgical technique for Laparoscopic Cholecystectomy

After the sub-umbilical incision, the surgical team created PP with 12 mmHg pressure by entering the abdomen with a veres needle. The patient was positioned in the reverse Trendelenburg position with the head 300 up. Subsequently, the same surgeon performed an LC with the appropriate surgical procedure.

Data collection

The severity of PONV was evaluated using the verbal descriptive scale (VDS). The classification of VDS is as follows: Grade: No PONV, Grade 1: mild PONV, Grade 2: moderate PONV, Grade 3: severe PONV. In our study, our follow-up parameters were defined as follows: Subjectively unpleasant sensation with awareness of the urge to vomit= nausea, forced expulsion of stomach contents from the mouth= Vomiting, attempted vomiting without stomach contents= retching, no postoperative nausea, vomiting or retching and no need for additional antiemetics= Complete response[2,7].

The total number of patients with nausea, vomiting, retching, or complete response was recorded during the first 0-6, 6-12, and 6-24 hours postoperatively. Antiemetic medication (10 mg metoclopramide) was administered if the VDS was above 2 or 3. A visual analgesic pain score (VAS) (no pain = 0, worst pain = 10) was used to evaluate pain. If VAS was higher than 3-4, the patients were given additional analgesics (10 mg/kg paracetamol IV). The need for additional analgesics in the postoperative period was chosen not only because it did not affect the incidence of PONV but also because tramadol and morphine were not preferred because they could increase the incidence of PONV. VDS, VAS, and the need for additional antiemetic and analgesic drugs were assessed between 0-6 hours, 6-12 hours, and 12-24 hours after discharge from the PACU. Patients had their VDS and VAS scores assessed by a blinded nurse unfamiliar with the study in the PACU. Patients were followed up in PACU by healthcare workers who were unaware of the study, and records were taken. Demographic data (age, weight, height, BMI), ASA scores, duration of surgery, gender, smoking, Apfel score, hemodynamic findings, additional antiemetic, VAS score, analgesic requirements, and adverse effects were recorded. Patients were closely monitored for adverse effects throughout the study. In the postoperative period, adverse effects (arrhythmia, hypotension, hypertension, laryngospasm, bronchospasm, respiratory depression, headache, dizziness, allergic reaction,

shivering, and pneumoperitoneum) were noted and managed accordingly.

The primary outcome is the incidence of PONV between 0-6, 6-12, and 6-24 hours postoperatively and the need for additional antiemetic requirements. The secondary outcome is detecting VAS scores, additional analgesic requirements needs, and adverse effects between 0-6, 6-12, and 6-24 hours postoperatively.

Statistical Analysis

The Statistical Package for Social Sciences SPSS 25.0 (I.B.M., Chicago, IL, U.S.A.) software was used for all statistical analyses. The Kolmogorov-Smirnov test tested the normality of the distributions of the data. Since the data was distributed non-normally in each group, non-parametric tests were used in the analysis. Descriptive statistics were given, and I will schedule some time for us to connect. Std. Dev. and median (min-max) for quantitative variables and n (%) for categorical variables. The Whitney U test for Fisher Exact and ChiSquare quantitative variables analyzed differences between aprepitant and granisetron groups. Chi-square tests were used to compare categoric variables between groups. Statistical significance was defined at $p<0.05$. The G Power 3.1.9 Sample Size Software was used to calculate the sample size. The minimum sample size required for the study was 26 patients in each group, totaling 52 patients to provide 80% test power at a 95% confidence level and effect size d=0.80 for the two-sided independent sample t-test.

Results

Sixty-one patients were recruited for the study. None of them were excluded. The patient allocation is outlined in the CONSORT flow diagram. They were randomly divided into Group A (n=31) and Group G (n=30) (Figure 1). Our study did not observe any difference between the groups regarding demographic characteristics (age, weight, height, BMI), ASA scores, duration of surgery, gender, smoking, and Apfel scores (Table I). The two groups had no statistically significant difference regarding MAP, HR, and SpO2.

In our study, the total incidence of PONV in the first 24 hours postoperatively was 6.5% in group A and 9.9% in group G, respectively. There was no statistically significant difference between groups A and G regarding VDS ($P>0.05$). Between the 30th and 60th minutes, PONV was observed in 5 (16.67%) patients in group G, while only 1 (3.23%) patient was in group A (p=0.10). Between the 30th and 60th minutes, a significantly lower VDS was observed in group A (VDS=0, 100%) compared to group G (VDS=0, 83.3%) (p=0.10) (Figure 2). Between the 60th and 90th minutes, 4 (13.33%) patients in group G had PONV, while none of the patients in the group A(0.0%) group had PONV (p=0.05) (Figure 2). There was no statistically significant difference between groups at other intervals until the 120th minute. Between the 6th and 12th hours, group A (VDS=0, 100%) had lower VDS than group G (VDS=0, 93.3%), but there was no statistically significant difference between the groups ($P>0.05$) (Figure 3).

Table I. — Patient demographics.

		Aprepitant (n=31)		Granisetron (n=30)		
		sd	Median (Min-max)	sd	Median (Min-max)	p*
Age (yr)		57.81±16.16	59 (18-90)	58.17±16.82	62.5 (23-81	0.857
Weight (kg)		78.58±16.04	80 (44-113)	74.97±12.04	75 (47-97)	0.374
Height (cm)		165.23±10.81	162 (149-188)	162.8±14.41	164.5 (110-181)	0.862
BMI (kg/cm2)		28.89±5.82	27 (18.8-41.6)	28.65±5.53	28.85 (16.7-45.5)	0.977
ASA (I-II)		2.03±.31	2 (1-3)	2.2±.41	2 (2-3)	0.079
Duration of surgery (min)		77.68±19.91	75 (55-150)	74.17±23.38	70 (30-120)	0.392
			n (%)		n (%)	p**
Gender	Female		21 (67.7)		18 (60.0)	0.529
	Male		10 (32.3)		12 (40.0)	
Smokers	No		17 (54.8)		18 (60.0)	0.684
	Yes		14 (45.2)		12 (40.0)	
Apfel score	0		4 (12.90)		6 (20.0)	0.731
	1		20 (64.52)		17 (56.67)	
	2		7 (22.58)		7 (23.33)	

p<0.05 significant; *Mann Whitney U test; **Chi-square or Fisher Exact Chi-square test.

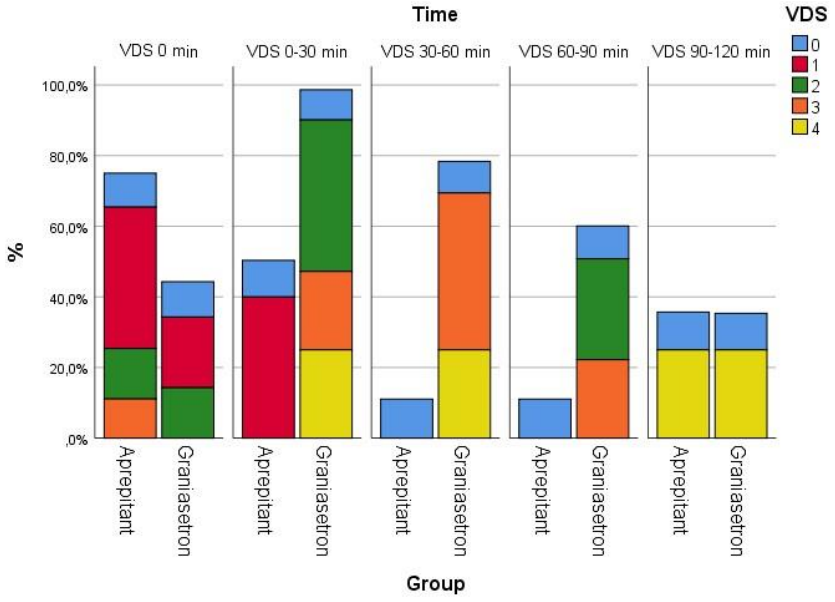

Fig. 2 — VDS between groups up to 120th minutes.
P>0.05; Chi-square or Fisher Exact Chi-square.

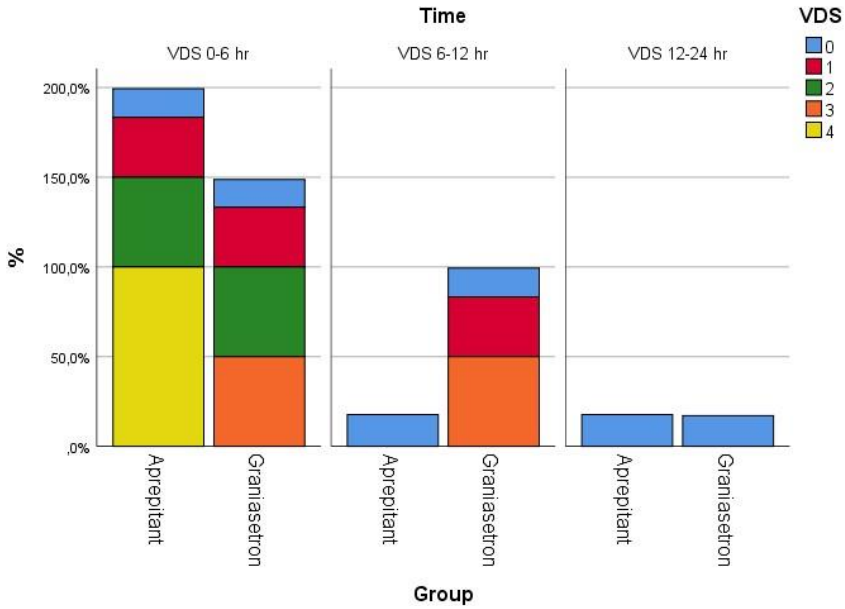

Fig. 3 — VDS between groups according to hours.
p>0.05; Chi-square or Fisher Exact Chi-square.

There was no statistically significant difference between the groups regarding additional antiemetic requirements at all times (p>0.05). Between the 30th and 60th minutes, 5 (16.6 %) patients in group G required additional antiemetic, while only 1 (3.2 %) patient in group A required additional antiemetic (p=0.10). Between the 60th and 90th minutes, 4 (13.3 %) patients in group G required additional antiemetic, while none (0.0%) in group A required additional antiemetic (p=0.05) (Figure 4). There was no statistically significant difference between the groups in terms of VAS scores (Figure 5). and additional analgesic requirements at all times (p>0.05) (Table II) (Figure 6).

Our study did not observe any statistically significant difference in patient adverse effects (arrhythmia, hypotension, hypertension, laryngospasm, bronchospasm, respiratory depression, headache, dizziness, allergic reaction, shivering, and pneumoperitoneum) between the two groups (Table III).

Discussion

Prevention and treatment of PONV are highly challenging and complex for the anesthesiologist and surgeon. PONV is a widespread finding due to patient, anesthetic, and surgical factors[5-7]. In conclusion, reducing the risk of PONV is a primary target in terms of patient satisfaction and features

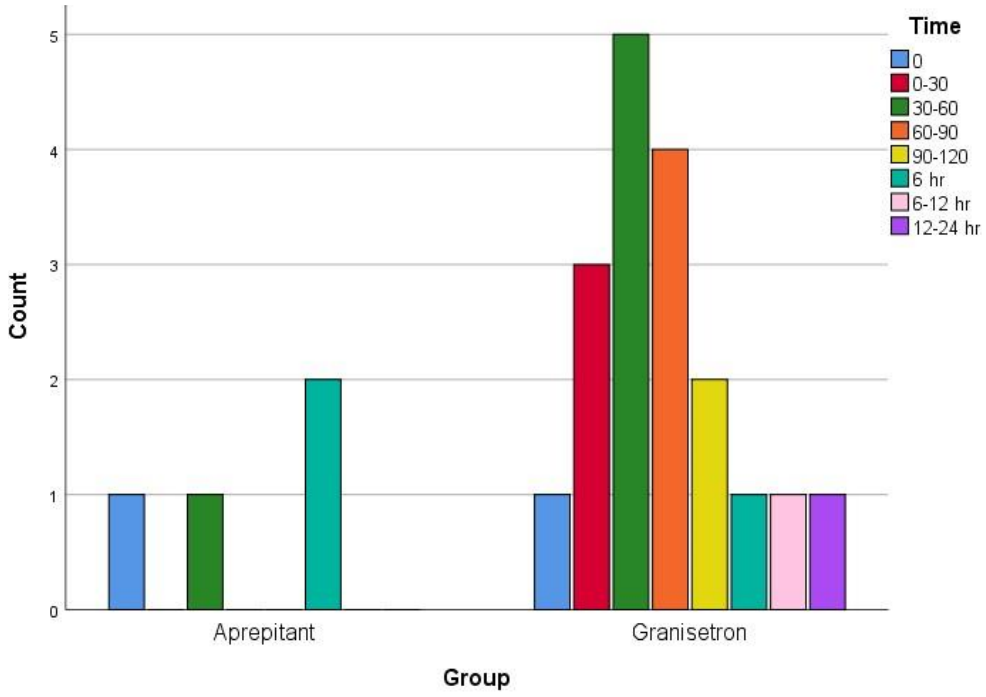

Fig. 4 — Additional antiemetics requirement in groups over time.
P=0.05 no statistical difference; Chi-square or Fisher Exact Chi-square.

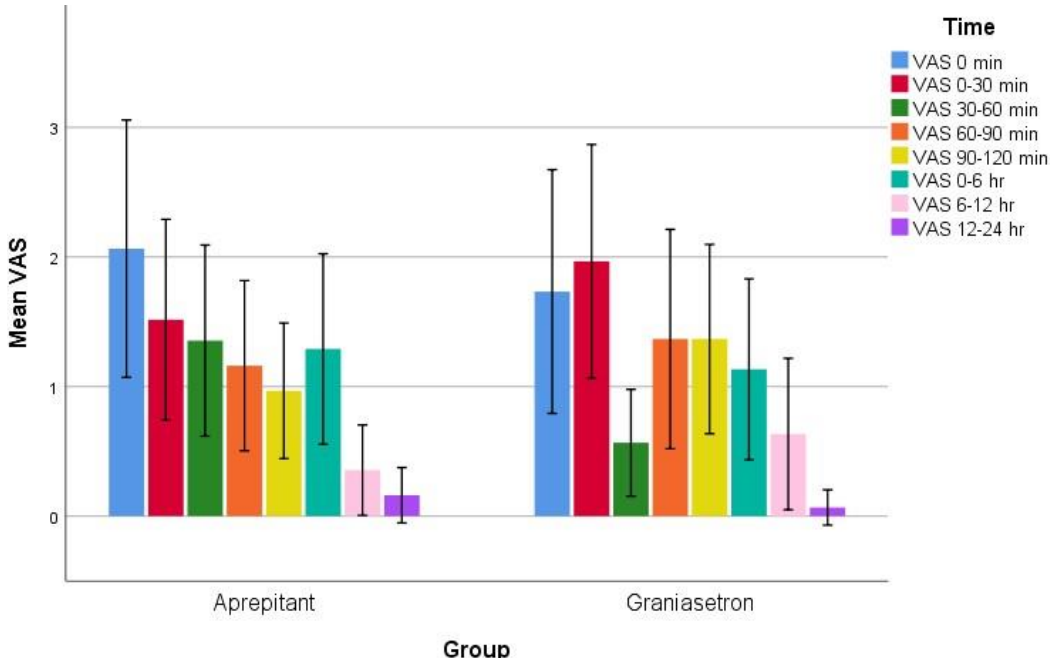

Fig. 5 — VAS in groups over time.
p>0.05; Chi-square or Fisher Exact Chi-square.

that stand out in Enhanced Recovery after Surgery (ERAS) protocols[6,7,9].

In recent years, many studies have compared the effect of aprepitant and serotonin 5-HT3 receptor antagonists in preventing PONV. Still, a direct comparison of granisetron (0.35-3 mg) and aprepitant (40, 80, and 125 mg) is not available in the literature. The current meta-analysis studies showed that doses of aprepitant effectively prevented PONV[4,6-8]. Aprepitant is approved for administration orally 1-3 hours before surgery. The essential advantages of aprepitant are its superior and potent antiemetic efficacy compared to other antiemetics, long action time, and low adverse effect profile[6-9].

Diemusch et al. reported that oral aprepitant was administered 40 mg, aprepitant 125 mg in a single dose, and IV ondansetron was administered 4 mg preoperatively in 922 patients undergoing major abdominal surgery. They reported that both aprepitant doses were significantly more effective than ondansetron in preventing vomiting 24 and 48

Table II. — Additional analgesic requirement in groups.

Additional analgesic Additional analgesic		Aprepitant (n=31) n(%)	Granisetron (n=30) n(%)	p
	None	28 (90.32)	25 (83.33)	0.337
	Yes	3 (3.23)	5 (16.67)	
Additional analgesic 0-30 min.	None Yes	30 (96.77) 1 (3.23)	26 (86.67) 4 (6.67)	0.323
Additional analgesic 30-60 min.	None Yes	27 (87.10) 4 (9.68)	30 (100.00) -	0.173
Additional analgesic 60-90 min.	None Yes	27 (87.10) 4 (9.68)	24 (80.00) 6 (16.67)	0.731
Additional analgesic 90-120 min.	None Yes	31 (100.00) -	26 (86.67) 4 (13.33)	0.053
Additional analgesic 0-6 hr.	None Yes	23 (74.19) 8 (6.45)	24 (80.00) 6 (16.67)	0.091
Additional analgesic 6-12 hr.	None Yes	29 (93.55) 2 (3.23)	27 (90.00) 3 (10.00)	0.481
Additional analgesic 12-24 hr.	None Yes	30 (96.77) 1 (3.23)	29 (96.67) 1 (3.33)	0.999
p<0.05 significant; Chi-square or Fisher Exact Chi-square.				

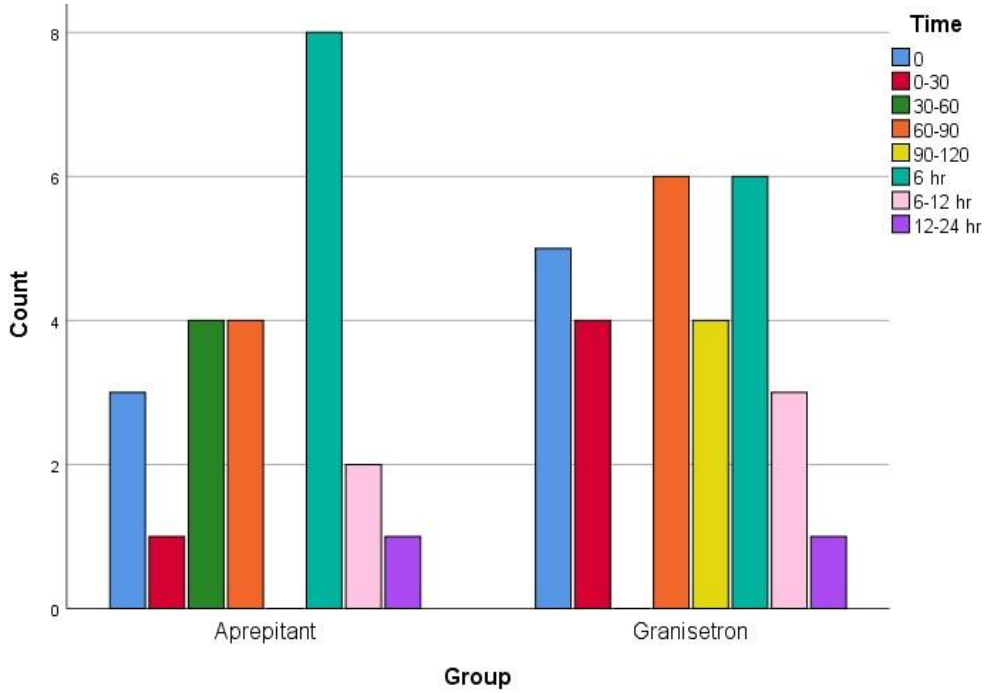

Fig. 6 — Additional analgesic requirement in groups over time.
p>0.05; Chi-square or Fsher Exact Chi-square.

hours after surgery and decreasing the severity of nausea in the first 48 hours after surgery (P<0.05)[4]. Diemunsch et al. suggested that NK1 receptor antagonists are effective, well-tolerated, safe, and non-toxic drugs[4]. Gan TJ et al. reported that in a multicenter study of 805 patients undergoing open abdominal surgery, 40 mg aprepitant, 125 mg aprepitant, or IV ondansetron 4 mg before surgery was administered. In this study, they showed that both doses of aprepitant were superior to ondansetron in preventing vomiting in the first 24-48 hours but reported no significant difference between ondansetron and aprepitant in terms of nausea control, rescue use, or complete response[5]. In our study, both groups had similar PONV changes at 0-6 hours.

Between the 30th and 60th minutes, PONV was observed in 5 (16.67%) patients in group G, while only 1 (3.23%) patient was in group A (p=0.10). Between the 60th and 90th minutes, 4 (13.33%)

Table III. — Adverse effects.

		Aprepitant (n=31) n (%)	Granisetron (n=30) n (%)	p
Arrhythmia	No	30 (96.8)	30 (100.0)	0.999
	Yes	1 (3.2)	-	
Hypotension	No	30 (96.8)	30 (96.7)	0.999
	Yes	1 (3.2)	-	
Hypertension	No	31 (100.0)	29 (96.7)	0.492
	Yes	-	1 (3.3)	
Laryngospasm	No	31(96.8)	30 (100.0)	NA
Bronchospasm	No	31 (100.0)	30 (100.0)	NA
Respiratory depression	No	31 (100.0)	30 (100.0)	NA
Headache	No	31 (100.0)	30 (100.0)	NA
Dizziness	No	31 (100.0)	30 (100.0)	NA
Allergic reaction	No	31 (100.0)	30 (100.0)	NA
Shivering	No	31 (100.0)	30 (100.0)	NA
Pneumoperitoneum	No	30 (96.8)	30 (100.0)	0.999
	Yes	1(3.2)		
p<0.05 significant; Chi-square or Fisher Exact Chi-square; NA: non available.				

patients in the granisetron group had PONV, while none of the patients in the aprepitant (0.0%) group had PONV (p=0.05) (Figure 2). We did not observe any statistically significant difference in VDS between groups A and G (P>0.05). Between the 30th-60th minutes, a significantly lower VDS was observed in Group A (VDS=0, 100%) compared to Group G (VDS=0, 83.3%) (p=0.10) (Figure 2). We did not observe any statistically significant difference between groups at other intervals until the 120th minute. Between the 6th and 12th hours, group A (VDS=0, 100%) had lower VDS than group G (VDS=0, 93.3%), but there was no statistically significant difference between the groups (P>0.05) (Figure 3).

Moon HY et al. reported that in a study of 93 patients undergoing laparoscopic gynecologic surgery under general anesthesia, administered IV palonosetron 0.075 mg or oral aprepitant 40 mg and the aprepitant group was not less to palonosetron regarding complete response 0 and 2 hours after administration and 0-48 hours after surgery. They reported that the severity of nausea was significantly less in the aprepitant group than in the palonosetron group (P<0.05)[10].

In our study, between the 30th and 60th minutes, a significantly lower VDS was observed in Group A (VDS=0, 100%) compared to Group G (VDS=0, 83.3%) (p=0.10) (Figure 2). Between the 6th and 12th hours, Group A had a lower VDS than Group G, but there was no statistically significant difference (P>0.05) (Figure 3). In the same study, they reported that analgesic consumption was significantly lower in the aprepitant group 6 and 24 hours after the application, compared to the palonosetron group, and more rescue analgesia was required in the aprepitant group[10]. In contrast to our study, Moon HY et al. found increased rescue analgesics in the aprepitant group. We did not observe a significant difference between the groups regarding VAS scores (Figure 5) and additional analgesic requirements at all times (p>0.05) (Table II) (Figure 6).

In a meta-analysis study, Murakami C et al. showed that oral aprepitant 40 mg and 80 mg were superior to 5-HT3 receptor antagonists in preventing PONV[11]. We compared 40 mg of oral aprepitant and 3 mg of granisetron in our study. As a result, in our study, a significantly lower VDS was observed in group A at the 30th-60th between minutes compared to group G (p=0.10) (Figure 2). Between the 6th and 12th hours, group A had a lower VDS than group G, but there was no statistically significant difference (P>0.05) (Figure 3).

Several meta-analyses comparing aprepitants with 5-HT3 receptor antagonists have shown that aprepitants have higher efficacy in preventing postoperative vomiting but lower efficacy in preventing nausea. It has been suggested that aprepitant should be administered orally at least one hour before surgery for efficacy[15-20]. In our study, we administered aprepitant orally one hour before the surgery. We observed a lower rate of PONV in the aprepitant group between the 30th-60th and 60th-90th minutes. We know that the administration of granisetron 10 minutes before extubation, compared to the aprepitant administration one hour before the

surgery, might also explain this difference in PONV in the first 30 minutes after surgery. The superior PONV score was higher in the granisetron group 30 minutes after surgery due to suboptimal application time.

There is limited data in the literature on the side effects associated with using aprepitant to prevent PONV. The most commonly reported adverse events are headache, hypotension, bradycardia, constipation, pruritus, pyrexia, and dizziness,[8,16,17] A significant QTc prolongation that can be observed with 5-HT3 antagonists is observed in aprepitant use has not been reported[16-18]. In our study, arrhythmia, hypotension, and hypertension were detected in only one patient each, and no adverse side effects were detected.

Aprepitant, which acts with an NK1 receptor antagonist, is more effective in reducing postoperative vomiting than nausea. This effect may be due to its affinity for NK1 receptors at peripheral and central levels. It is considered a useful prophylactic antiemetic in patients undergoing LC, being more effective alone or in combination with other antiemetics[5,10]. A single dose of oral aprepitant was more effective in reducing PONV, nausea severity, number of rescue antiemetics, and postoperative PONV incidence in group G, especially between the 30th and 60th minutes and the 60th and 90th minutes, but it did not reach statistical significance. However, we found that aprepitant had similar effects to granisetron in the 24 hours, especially preventing the time until the first emetic attack. There is no ideal agent for preventing PONV and commonly used traditional antiemetics have limited antiemetic effectiveness and side effects.

Limitations

Our study has some limitations. These are limited sample sizes, historical data on PONV, the absence of a control group, and 80 mg and 125 mg aprepitant groups combined with other drugs. The aprepitant is very expensive, and it is not easy to find the drug. Also, the preoperative Apfel scores are not very high (maximum 2) in the aprepitant group. Low preoperative Apfel scores might have contributed to reducing the actual effect of a potent drug like aprepitant.

Conclusion

We observed that aprepitant may be more effective than granisetron in preventing PONV and can be used safely in patients undergoing LC. Therefore, aprepitant can be added to multimodal PONV treatment as it has positive features such as long half-life, lack of sedation and QTc prolongation, and effective prevention of PONV. However, further research is needed to determine the optimal dose and rescue plans of aprepitant in preventing and treating PONV, its interaction with other antiemetics, its side effect profile, and its cost-effectiveness.

Authors' Contributions : B.N.G.: Data collection, Data analysis, Article writing. F.L.: Data analysis. A.U: Data analysis. M.Y.Ç.: Data analysis and statistical analysis. N.Ç.: Data analysis, Article writing and editing, Supervision. M.E.: Surgeon performing laparoscopic cholecystectomy.

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