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ORIGINAL INVESTIGATION

CYP2D6 isoenzyme and ABCB1 gene polymorphisms associated with postoperative nausea and vomiting in women undergoing laparoscopic cholecystectomy: a randomized trial

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Abstract
Introduction: Postoperative nausea and vomiting is still a common complication. Serotonin receptor antagonists are commonly used in clinical practice for antiemetic prophylaxis. Interindividual variations in drug response, including single nucleotide polymorphisms, are related to pharmacokinetic and pharmacodynamic changes in these drugs and may lead to a poor therapeutic response. This study aimed to evaluate the influence of CYP2D6 isoenzyme and ABCB1 gene polymorphisms on the frequency of postoperative nausea and vomiting with the use of ondansetron or palonosetron.
Methods: A randomized, double-blind clinical trial including 82 women aged 60 years or over undergoing laparoscopic cholecystectomy was conducted. Patients were randomized to receive either ondansetron or palonosetron for postoperative nausea and vomiting prophylaxis. DNA was extracted from saliva. Genetic polymorphisms were analyzed by real-time polymerase chain reaction. The following polymorphisms were analyzed: rs3892097 C/T, rs1128503 A/G, rs16947 A/G, rs1065852 A/G, rs1045642 A/G, rs2032582 C/A, and rs20325821 C/A.
Results: Overall, vomiting, and severe nausea occurred in 22.5% and 57.5% of patients, respectively. In the palonosetron group, patients with the GG genotype (rs16947 A/G) experienced more severe nausea (p = 0.043). In the ondansetron group, patients with the AA genotype (rs16947 A/G) presented mild nausea (p = 0.034), and those with the AA genotype (rs1065852 A/G) experienced more vomiting (p = 0.034).

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Conclusion: A low antiemetic response was observed with ondansetron in the presence of the AA genotype (rs16947 A/G) and the AA genotype (rs1065852 A/G), and a low therapeutic response was found with palonosetron in the presence of the GG genotype (rs16947 A/G) in laparoscopic cholecystectomy.
Register: ClinicalTrials.gov.

Introduction

Postoperative Nausea and Vomiting (PONV) is a frequent postoperative complication despite antiemetic prophylaxis. It affects approximately one third of patients[1] and may be associated with surgical complications. Additionally, PONV causes patient dissatisfaction, is as feared as postoperative pain, delays hospital discharge, and, consequently, increases hospitalization costs.[2,3]

The incidence of PONV in patients undergoing laparoscopic cholecystectomy has been reported to be 50—72% when no prophylactic antiemetic is provided.[4] Variables such as female sex and nonsmoking status are independent predictors of PONV.[5]

In clinical practice, 5-Hydroxytryptamine-3 (5-HT3) receptor antagonists are commonly used to prevent PONV in laparoscopic procedures. However, resistance to prophylaxis remains a problem and may be associated with genetic polymorphisms.[6,7]

Pharmacogenetics is a branch of genetics that deals with the individual response to drugs and drug metabolism.[8-10] Resistance to antiemetic prophylaxis is related to interindividual genetic variation of 5-HT3 receptor polymorphisms.[8-14] Two systematic reviews have observed an association of PONV with genetic polymorphisms.[15,16]

These polymorphisms include alterations in Adenosine triphosphate-Binding Cassette subfamily-B member 1 (*ABCB1*), which encodes P-glycoprotein, a drug transmembrane transporter acting on multiple tissues.[3] A variation in a single base pair in the DNA sequence (single nucleotide polymorphism, SNP) would lead to phenotype differences, which could result in changes in the function and expression of this transporter, affecting drug metabolism and action. CYP2D6, an isoenzyme of cytochrome P450 responsible for the metabolism of 5-HT3 receptor antagonists, also exhibits variations in gene expression that may result in changes in the biotransformation of these drugs, leading to a reduction in their effects.[17] Some of the SNPs in the ABCB1 gene related to different phenotypes of response to 5-HT3 receptor antagonists are C1236T (rs1128503), G2677T (rs2032582), and C3435T (rs1045642).[17]

This study aimed to evaluate the influence of CYP2D6 isoenzyme and ABCB1 gene polymorphisms on the frequency of PONV by comparing the use of 5-HT3 receptor antagonists (palonosetron vs. ondansetron) for PONV prophylaxis in laparoscopic cholecystectomy.

Methods

This is a prospective, randomized, double-blind, single-center clinical trial. The ethical approval for this study was provided by our institution, and the trial is registered at ClinicalTrials.gov. Eighty-two women undergoing laparoscopic cholecystectomy between November 2015 and November 2016 at our institution were consecutively recruited and provided written informed consent. Randomization to one of two groups was performed using GraphPad Prism Quickcalcs (GraphPad Software, Inc., La Toya, CA, USA).

Inclusion and exclusion criteria

Inclusion criteria were female sex, age 60 years or over, American Society of Anesthesiologists (ASA) physical status I, II, or III, being eligible for laparoscopic cholecystectomy under general anesthesia, and an 8- to 10-hour fast. Exclusion criteria were pregnancy, urgent surgery, motion sickness, history of nausea and vomiting in previous surgical procedures, Body Mass Index (BMI) > 35 $kg.m^{-2}$, and lifestyle habits such as smoking and alcoholism.

Sample size

This is a substudy of the original study entitled "Use of palonosetron and ondansetron in the prophylaxis of postoperative nausea and vomiting in women 60 years of age or older undergoing laparoscopic cholecystectomy: a randomized double-blind study".[18] In the original study, sample size was calculated on the basis of the primary outcome (nausea) and using previously published results as a reference.[19] Under the hypothesis of non-inferiority of palonosetron compared with standard ondansetron, a sample size of at least forty patients per treatment group was necessary to detect that 25% of patients in the ondansetron group and 48% in the palonosetron group would have nausea and vomiting, at a significance level of 5%, 80% power, and a maximum acceptable error of 5% equivalence.

Sample collection

Saliva samples were collected for DNA extraction before induction of anesthesia, stored in Falcon tubes, and kept frozen at -20°C. Genomic DNA was extracted from buccal epithelial cells at our clinical research unit. For this extraction process, Falcon tubes were centrifuged to form a pellet of buccal cells. The supernatant was discarded, and 1 mL of proteinase K solution was added. After incubation, undigested proteins were removed with the addition of ammonium acetate, and DNA was then precipitated with isopropyl alcohol. After centrifugation, the supernatant was discarded, the pellet was washed with decanted ethanol, and DNA was resuspended in extraction buffer (10 mM Tris-HCl; 1 mM EDTA, final volume of 50 mL). DNA concentration and

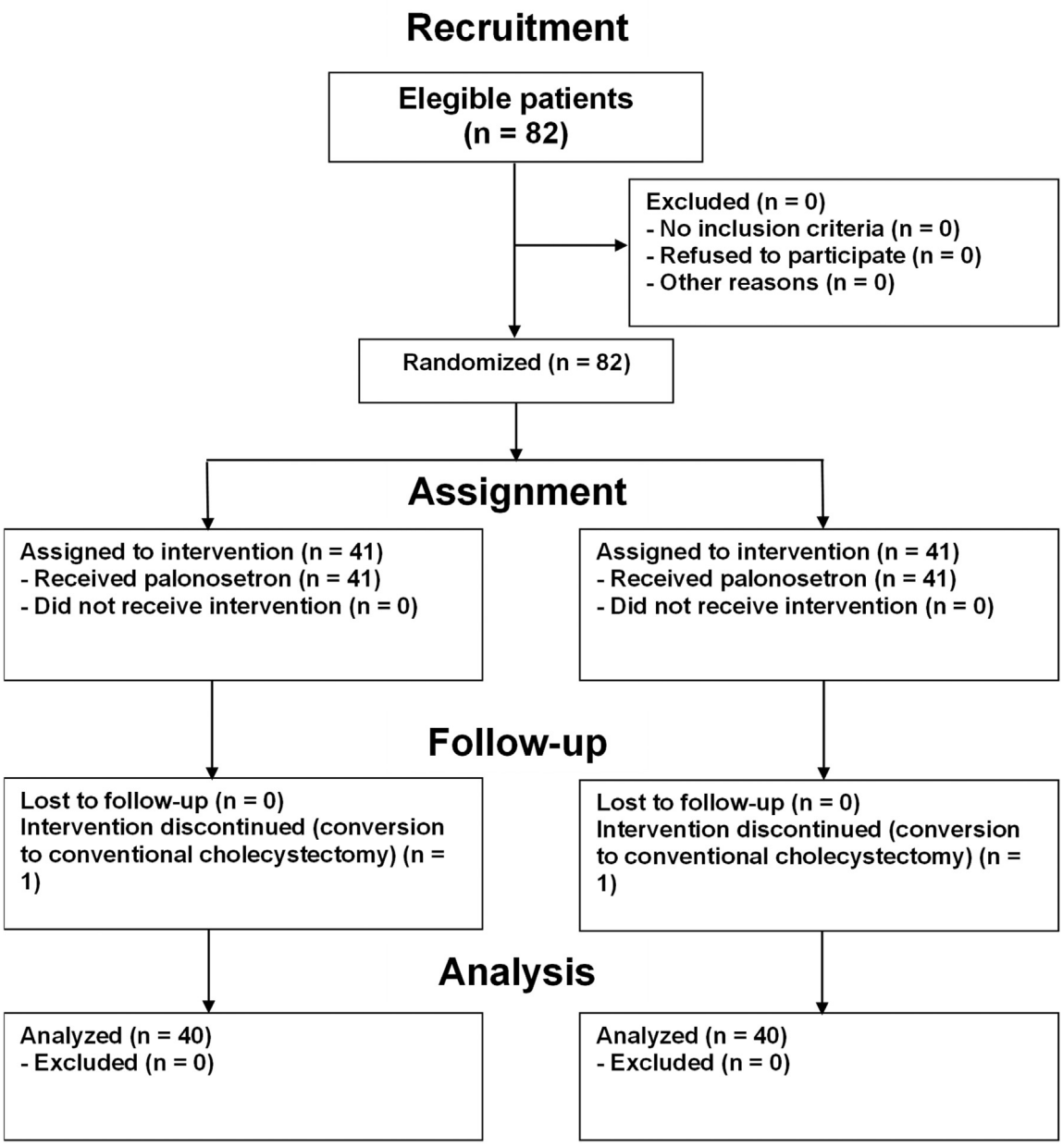

Figure 1 Study flowchart.

purity were determined by a NanoDrop 2000c spectrophotometer (Thermo Scientific™ NanoDrop 2000). DNA concentration was evaluated at 260 nm, and a 260/280 nm ratio was used to estimate DNA purity.[20] Polymerase Chain Reaction (PCR) was quantified in real time in a total volume of 4 μL (4 ng of DNA, 2 μL Taqman PCR master mix, 0.1 SNP; Applied Biosystems probe, Foster City, CA, USA). Amplifications were obtained by thermocycling consisting of an initial denaturation at 95°C for 10 minutes, followed by 40 cycles at 92°C for 15 seconds and 60°C for 1 minute. TaqMan real-time PCR was used for genotyping (Byosistems® 7500 Thermo Fisher Scientific, Foster City, CA, USA). The polymorphisms rs3892097 C/T, rs1128503 A/G, rs16947 A/G, rs1065852 A/G, rs1045642 A/G, rs2032582 C/A, and rs20325821 C/A were selected, evaluated, and tested as expected by Hardy-Weinberg proportions. Applied Biosystems SNP probes and master mix (Foster City, CA, USA) were used. Biological samples were discarded at the end of the study.

Anesthesia

After genetic material was collected, half of the patients randomly received palonosetron 75 mg, and the other half, ondansetron 4 mg. The solutions were prepared by an anesthesiologist not participating in the study and contained ondansetron or palonosetron in 5-mL syringes (0.9% saline was added to dilute the medication and even the volumes). They were then given to the blinded anesthesiologist 1 minute before the induction of Intravenous (IV) anesthesia. General anesthesia with tracheal intubation was performed according to the clinical protocol of the trial. Propofol 1–

2 mg.kg^{-1}, rocuronium 0.6 mg.kg^{-1}, fentanyl 3 μg.kg^{-1}, and lidocaine 1.5 mg.kg^{-1} were used for induction of IV anesthesia. Anesthesia was maintained with remifentanil 0.05 μg.kg^{-1}.min to 0.3 μg.kg^{-1}.min in a continuous IV infusion pump, and sevoflurane 1 to 3 MAC (minimum alveolar concentration) was used for maintenance of hypnosis with inspired concentration adjusted for a Bispectral Index (BIS) between 40–60. Additional IV doses of rocuronium one fourth of the initial dose were also administered as needed for muscle relaxation.

Before the end of surgery, IV parecoxib 40 mg, dipyrone 50 mg.kg^{-1}, and morphine 0.03 mg.kg^{-1} were administered for postoperative analgesia, and the surgical wound was infiltrated with 20 mL of 0.5% ropivacaine. The neuromuscular block was reversed with IV neostigmine 0.04 mg.kg^{-1} and atropine 0.02 mg.kg^{-1}, and the trachea was extubated.

In the ondansetron group, 4 mg every 8 hours was administered postoperatively by the nursing staff. In both groups, at medical discretion, IV metoclopramide 10 mg was used as rescue therapy for PONV. Patients received dipyrone 1g IV every 4 hours and parecoxib 40 mg IV every 12 hours in the first 48 hours after surgery. The patients had oral diet reintroduced 6 hours after surgery.

Postoperative evaluation

All participants received clinical visits by the research team at 2, 6, 24, and 48 hours after the end of laparoscopic surgery, when they were asked about the frequency and intensity of PONV and other adverse effects (headache, vertigo, and/or drowsiness). The primary outcome was a decrease in nausea and vomiting with antiemetic prophylaxis by comparing palonosetron with ondansetron in the presence of CYP2D6 isoenzyme and ABCB1 gene polymorphisms. The secondary outcome was the relationship of CYP2D6 isoenzyme and ABCB1 gene polymorphisms with nausea and vomiting. In this study, nausea was defined as the unpleasant and involuntary sensation of vomiting without expulsion of gastric contents and vomiting as the expulsion of contents of the stomach. The severity of episodes of PONV was measured on a numerical scale ranging from 0 to 10 (0 for no episodes and 10 for the worst possible sensation). A score greater than 5 was considered severe.

A Visual Analog Scale (VAS) was used to measure pain severity. This scale ranges from 0 to 10 (0 refers to no pain and 10 refers to the worst possible pain). Morphine at an IV dose of 0.03 mg.kg^{-1} was indicated in cases of pain $>$ 4 (moderate pain according to the VAS).

The principal investigator did not have access to prescriptions and medical records in the first 48 hours postoperatively because of the use of ondansetron every 8 hours and single use of palonosetron. After this period, the investigator analyzed the medical records and collected data regarding opioids and rescue therapy.

Statistical analysis

Eighty participants completed the study protocol. Numerical variables were described as mean and standard deviation or median and interquartile range. Categorical variables were described as absolute and relative frequencies. To compare numerical variables between groups, the Mann-Whitney test

Table 1 Clinical and surgical characterization of the sample according to study groups.

Variable[a]	Palonosetron (n = 40; 50%)	Ondansetron (n = 40; 50%)	*p*-value
Clinics			
Age (years)	65 (63–70) [66.8]	64 (61.3–70) [66]	0.41
Weight (kg)	66 (60–79.5) [68.6]	70 (60–76.8) [69.1]	0.70
Height (cm)	160 (155–165) [159]	160 (155–169) [162]	0.10
BMI (kg.m^{-2})	26.6 (23.9–29.9) [26.7]	26.3 (23.8–29.1) [26.5]	0.83
ASA			
I	2 (5.0)	7 (17.5)	
II	36 (90.0)	30 (75.0)	0.16
III	2 (5.0)	3 (7.5)	
Comorbidities			
SAH	34 (85.0)	29 (72.5)	0.17
DM2	9 (22.5)	9 (22.5)	1.00
Others	10 (25.0)	7 (17.5)	0.41
Surgery characteristics & drug doses			
Anesthesia duration (min)	115 (86–135) [122]	120 (91–135) [118]	0.70
Surgery duration (min)	89 (60–102) [90.8]	80 (61.8–95) [87.4]	0.92
Pneumoperitoneum duration (min)	50 (35–80) [63.5]	53.5 (41–73.8) [60.7]	0.84
Total dose of fentanyl (μg)	200 (200–240) [211]	205 (200–240) [214]	0.48
Total dose of remifentanil (μg)	334 (179–592) [440]	366 (28–606) [416]	0.89
Total dose of morphine (mg)	2 (2–2) [2.06]	2 (2–2) [2.03]	0.87
Volume of LR administered (mL)	1000 (750–1500) [1103]	1000 (1000–1000) [1084]	0.95

BMI, Body Mass Index; ASA, American Society of Anesthesiologists Physical Status; SAH, Systemic Arterial Hypertension; DM2, Diabetes Mellitus type 2; LR, Lactated Ringer's.
Categorical variables were compared by chi-square or Fisher's exact test, and numerical variables were compared by Mann-Whitney test.
[a] Described by median (25th–75th percentiles) or number of patients (%).

Table 2 Characterization of genotypes.

Variable	Total sample 80 (100%)	n	%
rs 3892097 C/T	55 (68.8 %)		
CC	x	47	85.5
CT		8	14.5
rs 1128503 A/G	49 (61.3 %)		
GG		27	55.1
AG		20	40.8
AA		2	4.1
rs 16947 A/G	60 (75.0 %)		
GG		14	23.3
AG		23	38.3
AA		23	38.3
rs 1065852 A/G	55 (68.8 %)	34	61.8
GG			
AG		18	32.7
AA		3	5.5
rs 1045642 A/G	66 (82.5 %)		
GG		38	57.6
AG		22	33.3
AA		6	9.1
rs 2032582 C/A	60 (75.0 %)		
CC		57	95.0
CA		0	0.0
AA		3	5.0
rs 20325821 C/A	60 (75.0 %)		
CC		29	48.3
CA		20	33.3
AA		11	18.3

Data are presented as number of patients (%).

(to assess the association between polymorphisms and presence of PONV), Pearson's Chi-Square test, or Fisher's exact test were used. In case of polytomous variables, adjusted residual analysis was used to find statistically significant associations. The level of significance was set at 5% ($p \leq 0.05$), and all analyses were performed in SPSS, version 21.0.

Results

This study recruited 82 eligible participants. After randomization, one patient in the palonosetron group (surgery was converted to the conventional technique) and one patient in the ondansetron group (the patient had uncontrollable vomiting that did not stop with rescue therapy) were excluded. Thus, 40 patients were analyzed in each group (Fig. 1).

There were no significant differences between the groups regarding age, physical status classification, and presence of associated diseases. The groups were also homogeneous in terms of surgical variables, such as duration of anesthesia, duration of surgery, duration of pneumoperitoneum, total dose of fentanyl, remifentanil, and morphine, and volume of crystalloid solution administered (Table 1).

There was no increase in opioid consumption in the postoperative period. Morphine was administered postoperatively to two patients (5.0%) in the palonosetron group and to one patient (2.5%) in the ondansetron group ($p = 0.99$).

More than 50% of participants experienced nausea within 48 hours, half of the cases being mild and the other half severe. Also, 22.5% of the participants experienced vomiting. There were no statistically significant differences between groups for nausea within 48 hours ($\chi^2 = 0.46$; $p = 0.497$), mild nausea ($\chi^2 = 0.00$; $p = 1.000$), severe nausea ($\chi^2 = 0.98$; $p = 0.393$), or vomiting ($\chi^2 = 3.51$; $p = 0.061$).

Table 2 shows the characterization of genotypes. SNPs rs1045642 A/G (82.5%), rs16947 A/G (75%), rs2032582 C/A (75%), and rs20325821 C/A (75%) were the most commonly found, respectively. Within rs1045642 A/G, the GG genotype was the most common (57.6%). Within rs16947 A/G, the AG and AA genotypes were the most frequently found (38.3% each). Within rs2032582 C/A and rs20325821 C/A, the CC genotype was the most prevalent (95% and 48.3%, respectively). No statistically significant differences were found between groups in terms of genotypes, as shown in Table 3.

In the palonosetron group, patients with the GG genotype (rs16947 A/G) had a significantly higher presence of severe nausea ($p = 0.043$) compared to patients with the AG and AA genotypes, as shown in Table 4. In the ondansetron group, patients with the AA genotype (rs16947 A/G) had a significantly higher prevalence of mild nausea than patients with the GG and AG genotypes ($p = 0.034$). Moreover, those with

Table 3 Prevalence of genotypes according to study groups.

Variable	Palonosetron	Ondansetron	*p*-value
rs3892097 C/T			1.000[b]
CC	22 (84.6)	25 (86.2)	
CT	4 (15.4)	4 (13.8)	
rs1128503 A/G			0.212[a]
GG	16 (64.0)	11 (45.8)	
AG	9 (36.0)	11 (45.8)	
AA	0 (0.0)	2 (8.3)	
rs16947 A/G			0.216[a]
GG	5 (15.6)	9 (32.1)	
AG	12 (37.5)	11 (39.3)	
AA	15 (46.9)	8 (28.6)	
rs1065852 A/G			0.640[a]
GG	18 (60.0)	16 (64.0)	
AG	11 (36.7)	7 (28.0)	
AA	1 (3.3)	2 (8.0)	
rs1045642 A/G			0.941[a]
GG	19 (55.9)	19 (59.4)	
AG	12 (35.3)	10 (31.3)	
AA	3 (8.8)	3 (9.4)	
rs2032582 C/A			1.000[a]
CC	29 (93.5)	28 (96.6)	
CA	0 (0.0)	0 (0.0)	
AA	2 (6.5)	1 (3.4)	
rs20325821 C/A			0.587[a]
CC	16 (50.0)	13 (46.4)	
CA	9 (28.1)	11 (39.3)	
AA	7 (21.9)	4 (14.3)	

Data are presented as number of patients (%).
[a] Pearson's chi-square test.
[b] Fisher's exact test.

Table 4 Association of polymorphisms with nausea and vomiting in the palonosetron group.

Polymorphism	n	Nausea within 48 hours	Mild nausea	Severe nausea	Vomiting
		n (%)	n (%)	n (%)	n (%)
rs 3892097 C/T					
CC	22	13 (59.1)	6 (27.3)	7 (31.8)	6 (27.3)
CT	4	2 (50.0)	1 (25.0)	1 (25.0)	1 (25.0)
p-value		1.000[b]	1.000[b]	1.000[b]	1.000[b]
rs 1128503 A/G					
GG	16	9 (56.3)	5 (31.3)	4 (25.0)	3 (18.8)
AG	9	6 (66.7)	3 (33.3)	3 (33.3)	2 (22.2)
p-value		0.691[b]	1.000[b]	0.673[b]	1.000[b]
rs 16947 A/G					
GG	5	5 (100)	1 (20.0)	4 (80.0)	3 (60.0)
AG	12	7 (58.3)	5 (41.7)	2 (16.7)	2 (16.7)
AA	15	7 (46.7)	2 (13.3)	5 (33.3)	4 (26.7)
p-value		0.109[a]	0.231[a]	**0.043**[a]	0.191[a]
rs 1065852 A/G					
GG	18	9 (50.0)	3 (16.7)	6 (33.3)	5 (27.8)
AG	11	8 (72.7)	3 (27.3)	5 (45.5)	4 (36.4)
AA	1	1 (100)	1 (100)	0 (0.0)	0 (0.0)
p-value		0.340[a]	0.147[a]	0.597[a]	0.711[a]
rs 1045642 A/G					
GG	19	11 (57.9)	5 (26.3)	6 (31.6)	4 (21.1)
AG	12	7 (58.3)	3 (25.0)	4 (33.3)	4 (33.3)
AA	3	2 (66.7)	1 (33.3)	1 (33.3)	1 (33.3)
p-value		0.959[a]	0.958[a]	0.994[a]	0.723[a]
rs 2032582 C/A					
CC	29	16 (55.2)	6 (20.7)	10 (34.5)	7 (24.1)
AA	2	2 (100)	2 (100)	0 (0.0)	1 (50.0)
p-value		0.497[b]	0.060[b]	1.000[b]	0.456[b]
rs 20325821 C/A					
CC	16	8 (50.0)	4 (25.0)	4 (25.0)	2 (12.5)
CA	9	6 (66.7)	3 (33.3)	3 (33.3)	5 (55.6)
AA	7	4 (57.1)	1 (14.3)	3 (42.9)	3 (42.9)
p-value		0.721[a]	0.683[a]	0.688[a]	0.063[a]

[a] Pearson's Chi-Square test.
[b] Fisher's exact test; adjusted residual analysis at 5% significance.

the AA genotype (rs1065852 A/G) had a significantly higher presence of vomiting compared to those with the GG genotype ($p = 0.034$), as shown in Table 5.

Discussion

The present study suggests that ABCB1 gene and CYP2D6 isoenzyme polymorphisms have a genetic predisposition that interferes with the response of 5-HT3 receptor antagonists to PONV prophylaxis. In 2017, Song et al.[21] (2017) observed that the ABCB1 2677TT polymorphism was linked to increased nausea and vomiting with the use of palonosetron in spinal surgery. Our results revealed a statistically significant association between the GG genotype (rs16947 A/G) and the presence of severe nausea ($p = 0.043$) in the palonosetron group, which may lead to avoiding to prescribe palonosetron in this setting.

In the ondansetron group, the AA genotype (rs16947 A/G) was associated with mild nausea ($p = 0.034$), while the AA genotype (rs1065852 A/G) was associated with vomiting ($p = 0.034$). The results suggest that an alternative to ondansetron should be considered in the presence of these polymorphisms. Choi et al.[22] (2010) evaluated the use of ondansetron for PONV prophylaxis and showed that 35% of participants had PONV associated with polymorphisms. They found that altered drug pharmacokinetics was related to ABCB1 genotypes. He et al.[23] (2014) reached the same conclusion in a study of patients undergoing cancer treatment. Kim et al.[20] (2015) observed that ondansetron was less effective for PONV prophylaxis in the presence of -100_-102AAG polymorphisms of the 5-HT3B gene.

In the present study, vomiting and severe nausea occurred, respectively, in 22.5% and 28.8% of patients despite antiemetic prophylaxis, consistent with the rates reported by Gan et al.[24] (2006). The prevalence of the rs1045642 A/G polymorphism, found in 82.5% of the sample, did not correlate with increased PONV. The incidence of severe nausea and vomiting could have been higher if higher doses of opioids had been used. The presence of rs16947

Table 5 Association of polymorphisms with nausea and vomiting in the ondansetron group.

Polymorphism	n	Nausea within 48 hours	Mild nausea	Severe nausea	Vomiting
		n (%)	n (%)	n (%)	n (%)
rs 3892097 C/T					
CC	25	13 (52.0)	7 (28.0)	6 (24.0)	3 (12.0)
CT	4	2 (50.0)	0 (0.0)	2 (50.0)	1 (25.0)
p-value		1.000[b]	0.546[b]	0.300[b]	0.467[b]
rs 1128503 A/G					
GG	11	4 (36.4)	3 (27.3)	1 (9.1)	1 (9.1)
AG	11	8 (72.7)	4 (36.4)	4 (36.4)	1 (9.1)
AA	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
p-value		0.078[a]	0.572[a]	0.217[a]	0.906[a]
rs 16947 A/G					
GG	9	5 (55.6)	2 (22.2)[c]	3 (33.3)	1 (11.1)
AG	11	4 (36.4)	1 (9.1)[c]	3 (27.3)	1 (9.1)
AA	8	5 (62.5)	5 (62.5)[c]	0 (0.0)	0 (0.0)
p-value		0.489[a]	**0.034**[a]	0.206[a]	0.640[a]
rs 1065852 A/G					
GG	16	6 (37.5)	5 (31.3)	1 (6.3)	0 (0.0)[c]
AG	7	5 (71.4)	2 (28.6)	3 (42.9)	2 (28.6)[c]
AA	2	1 (50.0)	0 (0.0)	1 (50.0)	1 (50.0)[c]
p-value		0.325[a]	0.650[a]	0.071[a]	**0.034**[a]
rs 1045642 A/G					
GG	19	9 (47.4)	7 (36.8)	2 (10.5)	2 (10.5)
AG	10	7 (70.0)	2 (20.0)	5 (50.0)	1 (10.0)
AA	3	1 (33.3)	0 (0.0)	1 (33.3)	1 (33.3)
p-value		0.393[a]	0.330[a]	0.062[a]	0.518[a]
rs 2032582 C/A					
CC	28	16 (57.1)	10 (35.7)	6 (21.4)	3 (10.7)
AA	1	1 (100)	0 (0.0)	1 (100)	1 (100)
p-value		1.000[b]	1.000[b]	0.241[b]	0.138[b]
rs 20325821 C/A					
CC	13	6 (46.2)	4 (30.8)	2 (15.4)	1 (7.7)
CA	11	6 (54.5)	2 (18.2)	4 (36.4)	2 (18.2)
AA	4	2 (50.0)	1 (25.0)	1 (25.0)	0 (0.0)
p-value		0.920[a]	0.777[a]	0.497[a]	0.537[a]

[a] Pearson's Chi-Square test.
[b] Fisher's exact test.
[c] Equal letters do not differ by the adjusted residual analysis at 5% significance.

polymorphisms was associated with increased nausea in both groups, thus constituting a risk factor. Stamer et al.[25] (2019) identified the 5-HTTLPR rs4795541 polymorphism as an independent factor for PONV. The Brazilian sample used in this study is extensively diverse, and such diversity may influence the results of pharmacogenomic studies. More than 90 different CYP2D6 alleles have already been described, which makes screening for each drug complex.[26,27]

Although 5-HT3 receptor antagonists are commonly used in clinical practice for PONV prophylaxis in laparoscopic procedures, the incidence of nausea and vomiting remains high,[22] which may be related to genetic polymorphism.[25,28-30] As suggested by Janicki et al.,[30] (2011) understanding the effects of different drugs on polymorphic variants may be helpful in clinical practice.

The current study has several limitations that must be considered. This is a sub study with potential bias and weak potential for non-clinically relevant effects. The sample size was small, and the population was heterogeneous, few polymorphisms were analyzed, and only a single antiemetic prophylaxis was used. Also, only female patients were recruited, and patients with a previous history of nausea and vomiting were excluded. In addition, some degree of subjective error is inevitable in assessing intensity of nausea.

Conclusions

Our results suggest that genetic polymorphisms may influence the outcomes of antiemetic prophylaxis for PONV with 5-HT3 receptor antagonists. This interference may be linked to the SNP GG rs16947 A/G with palonosetron and the SNPs AA rs16947 A/G and AA rs1065852 with ondansetron. Nonetheless, our findings may contribute to the search for the optimal prophylactic approach to PONV, providing more information about the complexity of genetic effects on

PONV treatment. Genetic analysis may be useful for an improved pharmacological approach, and more studies on genotyping are needed.

Conflicts of interest

The authors declare no conflicts of interest.

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