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ORIGINAL RESEARCH

OPRM1 A118G Polymorphism and Ondansetron Efficacy for Postoperative Nausea and Vomiting in Laparoscopic Gynaecological Surgery: A Retrospective Cohort Study

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Background: The OPRM1 A118G polymorphism has been implicated in modulating susceptibility to postoperative nausea and vomiting (PONV). Ondansetron, a 5-HT3 receptor antagonist, is widely utilized for PONV prophylaxis; however, whether its efficacy is influenced by OPRM1 A118G polymorphism remains unclear.

Methods: We conducted a retrospective cohort study including patients undergoing laparoscopic gynecological surgery between January 2019 and December 2024; propensity score matching was used to adjust for confounders. OPRM1 A118G genotypes (AA, AG, GG) were analyzed through polymerase chain reaction and sequencing. PONV incidence and severity were assessed using the Visual Analog Scale (VAS) at various postoperative time points.

Results: The Ondansetron group had significantly lower PONV incidence within 2 hours (38.82% vs 56.98%, $p = 0.0174$) and 2 ~ 24 hours (8.24% vs 19.77%, $p = 0.0300$). The OPRM1 A118G polymorphism was associated with higher PONV risk, particularly in patients with the AG/GG genotypes in the control group. In the Ondansetron group, the association was significant only within 2 hours ($p = 0.0460$).

Conclusion: The OPRM1 A118G polymorphism is associated with an increased risk of early PONV, particularly in patients with the G allele, which has been related to reduced μ-opioid receptor sensitivity and increased opioid requirements, thereby predisposing patients to a higher PONV risk. Ondansetron significantly reduces PONV incidence and severity, especially in patients with higher genetic susceptibility.

Keywords: postoperative nausea and vomiting, OPRM1, A118G, ondansetron

Introduction

Postoperative nausea and vomiting (PONV) occur within 24 ~ 48 hours after surgery, affecting approximately 30% of patients.[1,2] As the most common complication following anesthesia, PONV lead to dehydration, wound dehiscence, prolonged hospital stays, and increased healthcare costs.[3,4] It is also a major cause of patient dissatisfaction post-surgery.[5]

The pathophysiology of PONV is complex, involving interactions between both the peripheral and central nervous systems.[6] Peripherally, surgical trauma and anesthetic agents trigger the release of neurotransmitters, including serotonin, in the gastrointestinal tract, which transmits afferent signals to the medullary vomiting center via the vagus nerve.[7] Centrally, the vomiting center integrates input from the vestibular system, chemoreceptor trigger zone (CTZ), and cerebral cortex, with the CTZ being particularly responsive to emetogenic substances, such as opioids and metabolites of inhaled anesthetics.[8] The emetic reflex is modulated by multiple neurotransmitter systems, including dopamine D2,

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5-hydroxytryptamine 3 (5-HT3), histamine H1, muscarinic, and neurokinin-1 (NK1) receptors. In addition, factors such as the type of surgical procedure, intraoperative hypotension leading to cerebral hypoperfusion, interindividual variability, and the administration of postoperative opioids have been identified as contributing to the activation of the emetic pathway.[9,10]

Recent studies on genetic single-nucleotide polymorphisms (SNPs) have provided significant insights into susceptibility to PONV. While genome-wide association studies have not identified high-impact susceptibility loci for PONV, increasing evidence indicates that genes related to dopamine receptors, particularly DRD2, play a crucial role in modulating dopaminergic neurotransmission within the chemoreceptor trigger zone and vomiting center, which are key components of the emetic reflex pathway.[11,12] The DRD2 TaqIA polymorphism (rs1800497) has been reported to alter dopamine receptor density and signaling efficiency, thereby influencing individual susceptibility to PONV and responsiveness to dopamine receptor antagonists. Several studies have confirmed this association, supporting the contribution of dopaminergic pathways to the pathophysiology of PONV.[2,12,13] Furthermore, the OPRM1 A118G (rs1799971) polymorphism, a key regulator of pain perception and opioid response, has been shown to indirectly influence PONV susceptibility.[14,15] The G allele at this locus results in impaired N-glycosylation of the μ-opioid receptor and reduces its binding affinity for endogenous and exogenous opioids, leading to diminished analgesic effects and a consequent need for higher opioid doses to achieve adequate pain control.[15–17] This increased opioid exposure represents an independent risk factor for PONV, linking the OPRM1 genotype to both analgesic efficacy and postoperative emetic risk. Consequently, the OPRM1 A118G polymorphism may serve as a genetic biomarker for predicting PONV risk, facilitating the development of personalized antiemetic strategies.

Ondansetron, a 5-HT3 receptor antagonist, is a critical drug for preventing PONV, especially in laparoscopic gynecological surgeries.[18,19] Recent studies have demonstrated that the monotherapy efficacy of ondansetron is approximately 50 ~ 60%, whereas its combination with dexamethasone reduces the incidence of PONV to 12.5%.[20] Individual responses to treatment may be influenced by genetic polymorphisms. The OPRM1 A118G polymorphism, which alters μ-opioid receptor function, has been shown to affect opioid sensitivity, a key factor contributing to the development of PONV.[15,16] It has been suggested that individuals with the OPRM1 118G allele, particularly women, require higher opioid doses, and the effectiveness of ondansetron in preventing PONV may be limited in this group.[5] The aim of the present study is to investigate the differences in the incidence and severity of PONV following ondansetron administration in patients with different OPRM1 A118G genotypes (AA/AG/GG) undergoing laparoscopic gynecological surgery.

Materials and Methods

Participants

This study was a retrospective analysis conducted at March 2025. The patients who underwent laparoscopic gynecological surgery at our institution were included, comprising those who did not receive Ondansetron intervention between January 2019 and December 2021 (Control group) and those who received Ondansetron between January 2022 and December 2024 (Ondansetron group). In our institution, ondansetron was introduced into routine prophylactic use for PONV only after January 2022. Therefore, patients from 2019–2021 naturally formed the control cohort, and those from 2022–2024 constituted the ondansetron cohort. This temporal grouping reflected an institutional practice change rather than a prospective intervention. The patients in the control groups were screened according to propensity score matching using R Studio, with the following covariates: age, BMI, ASA classification, type of underlying disease, anesthesia duration, pneumoperitoneum time, intraoperative blood loss, and total fentanyl dosage. Propensity score matching (PSM) was conducted using a 1:1 nearest-neighbor algorithm with a caliper width of 0.05. The selection of these covariates was based on their potential influence on PONV and anesthetic response. The balance between matched groups was evaluated using standardized mean differences (SMDs), with values <0.1 considered acceptable Average SMD before matching was 0.11; average SMD value after matching was 0.08. The study was approved by Shandong Provincial Hospital

Affiliated to Shandong First Medical University (#2025-03-207). Given the retrospective design and use of de-identified data, the requirement for individual informed consent was waived.

The Inclusion Criteria for the Patients Who Underwent Elective Laparoscopic Gynecological Surgery

The patients who met the inclusion criteria were included for analysis: Age ≥ 18 years; American Society of Anesthesiologists (ASA) classification I–II.

The Exclusion Criteria for the Patients Who Underwent Elective Laparoscopic Gynecological Surgery

If the patients met the exclusion criteria, they were exclude from analysis: Inability to understand the Visual Analog Scale (VAS) for pain assessment; Administration of antiemetics or occurrence of nausea and vomiting within 24 hours before surgery; History of allergy to any study-related medications; Use of chemotherapy agents within one week before surgery; Development of severe postoperative complications; History of smoking; History of gastrointestinal ulcers; Use of antitussive drugs or opioids with contraindications to neuroblocking within one week before surgery.

The Assessment of the Incidence and Severity of PONV

In our institution, PONV is routinely assessed and documented by trained anesthesiology nurses and ward physicians as part of standard postoperative care. The assessment is performed at standardized postoperative intervals (0–2 hours and 2–24 hours) according to the institutional monitoring protocol. The incidence and severity of PONV were recorded on postoperative days 1, 2, and 3 in the electronic medical record system. Only patients with complete PONV documentation were included in the analysis. Complete response (CR) was defined as the absence of vomiting without the need for rescue interventions, while complete control (CC) was defined as the absence of both vomiting and nausea. The CR rate (number of CR events/total number of cases) and the CC rate (number of CC events/total number of cases) were calculated. The severity of PONV was evaluated using the VAS,[21] with scores ranging from 0 to 10. A score of < 4 was categorized as mild, 4 ~ 7 as moderate, and > 7 as severe. All VAS data used in this study were extracted from routinely recorded postoperative nursing documentation.

The Identification of OPRM1 A118G

Preoperative blood samples routinely collected for standard laboratory testing were retrieved from the institutional biobank for genetic analysis after obtaining ethics committee approval. No additional blood collection was performed for this study. Preoperative blood samples were collected in tubes containing potassium ethylenediaminetetraacetate. Genomic DNA was extracted using the nucleic acid extraction Midi kit (TIANGEN, Beijing, China) according to the manufacturer's instructions. The extracted genomic DNA was stored at −20°C. Polymerase chain reaction (PCR) amplification was carried out as follows: (1) denaturation at 94°C for 5 minutes; (2) 30 cycles of 94°C for 30 seconds, 56°C for 30 seconds, and 72°C for 30 seconds; (3) final extension at 72°C for 5 minutes; (4) the reaction was held at 4°C. The primers used for PCR amplification were as follows: forward primer, OPRM1-A118G-F, 5'-CACTGATGCCTTGGCGTACTC-3'; reverse primer, OPRM1-A118G-R, 5'-GGAGGGCACAGGCTGTCT-3'. Additionally, a subsequent pyrosequencing analysis employed an extension primer: OPRM1-A118G-S, 5'-GCATGGGTCGGACAGG-3'. The PCR products were purified and sequenced using the ABI3130 sequencer (Applied Biosystems, USA). Sequencing reagents were also provided by Applied Biosystems. The sequencing data were analyzed using Chromas software.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics (version 22.0, IBM Corp., NY, USA). Descriptive data are presented as frequencies, percentages, and means ± standard deviations. Continuous variables were compared using Student's *t*-test or Mann–Whitney *U*-test as appropriate. Categorical variables were compared using Pearson's chi-square

test or Fisher's exact test. The relationship between gene variants and disease risk was assessed using unconditional logistic regression, with odds ratios (ORs) and 95% confidence intervals (CIs). Hardy-Weinberg equilibrium was used to calculate expected variant frequencies in the control group. Pairwise linkage disequilibrium (LD) (D' and r^2 values) and haplotype frequencies were determined with HAPLOVIEW version 4.2 (Broad Institute, Cambridge, MA), using the CI block definition. To control for type I errors arising from multiple comparisons across genotypes and time points, p-values were adjusted using the Bonferroni correction. The selection of statistical tests was based on data distribution and variable type. A P-value < 0.05 was considered statistically significant.

Results

Inclusion Process of the Recipients

The selection process began with 155 patients in the control group who underwent laparoscopic gynecological surgery between January 2019 and December 2021, and 152 patients in the Ondansetron group who underwent surgery between January 2022 and December 2024, as shown in Figure 1. Following the application of exclusion criteria, including missing data and specific comorbidities, 38 patients from the control group and 37 patients from the Ondansetron group were excluded, resulting in 117 patients in the control group and 115 patients in the Ondansetron group. Propensity score matching was subsequently conducted with a caliper value of 0.05, 86 patients from the control group and 85 from the Ondansetron group were retained for the final analysis. Post-matching standardized mean differences for all covariates were <0.1, confirming adequate group balance.

The Comparison of Baseline Clinical Characteristics of the Study Cohort

The baseline clinical characteristics of the study cohort were compared, comprising 86 patients in the control group and 85 patients in the Ondansetron group (Table 1). The mean age of patients in the control group was 32.97 ± 7.24 years, while the Ondansetron group had a mean age of 33.13 ± 8.06 years ($p = 0.8886$). The mean body mass index (BMI) was 23.76 ± 2.33 kg/m^2 in the control group and 24.02 ± 2.51 kg/m^2 in the Ondansetron group ($p = 0.4838$). The distribution of ASA classifications was similar between these two groups, with 56.98% of patients in the control group and 55.29% in the Ondansetron group classified as ASA I ($p = 0.8780$). In terms of primary diseases, no significant differences were observed between these two groups, with comparable proportions of benign ovarian masses, infertility, and ectopic

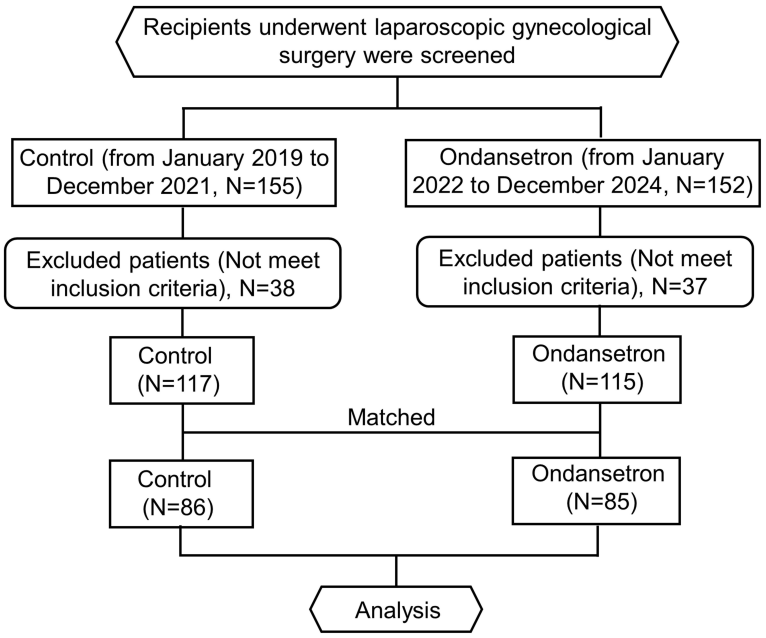

Figure 1 The inclusion process of the recipients who underwent laparoscopic gynecological surgery between the control group and the ondansetron group.

Table 1 Baseline Clinical Characteristics of the Study Cohort

Characteristics	Control (N=86)	Ondansetron (N=85)	*p* Value
Age (years)[a]	32.97 ± 7.24	33.13 ± 8.06	0.8886
Body mass index (kg/m^2) [a]	23.76 ± 2.33	24.02 ± 2.51	0.4838
ASA class[b]			
I	49 (56.98%)	47 (55.29%)	0.8780
II	37 (43.02%)	38 (44.71%)	
Primary disease[b]			
Benign ovarian masses	34 (39.53%)	32 (37.65%)	0.9302
Infertility	39 (45.35%)	41 (48.23%)	
Ectopic pregnancy	13 (15.12%)	12 (14.12%)	
Anesthesia duration (min)[a]	92.82 ± 28.65	95.47 ± 24.86	0.5194
Pneumoperitoneum time (min)[a]	62.14 ± 17.23	61.32 ± 17.15	0.7559
Intraoperative blood loss (mL)[a]	1026.35 ± 224.09	986.72 ± 215.36	0.2401
Fentanyl dosage (mg)[a]	0.27 ± 0.03	0.26 ± 0.04	0.0986

Notes: [a]Values were presented as Mean ± SD; [b]Values were presented as N (%).
Abbreviation: ASA, American Society of Anesthesiologists.

pregnancy (p = 0.9302). The mean anesthesia duration was 92.82 ± 28.65 minutes for the control group and 95.47 ± 24.86 minutes for the ondansetron group (p = 0.5194), while pneumoperitoneum times were 62.14 ± 17.23 minutes for the control group and 61.32 ± 17.15 minutes for the ondansetron group (p = 0.7559). Intraoperative blood loss was 1026.35 ± 224.09 mL in the control group and 986.72 ± 215.36 mL in the ondansetron group (p = 0.2401). The mean fentanyl dosage administered was 0.27 ± 0.03 mg in the control group and 0.26 ± 0.04 mg in the ondansetron group (p = 0.0986). This confirmed that baseline characteristics were well balanced following PSM.

The Incidence and Severity of PONV at Different Times After Surgery

The incidence and severity of PONV at different postoperative intervals (0–2 h and 2–24 h) were compared between the control and Ondansetron groups (Table 2). These time intervals were selected according to the institutional protocol, which distinguishes early and delayed PONV phases. The incidence of PONV within the first 2 hours postoperatively was significantly lower in the ondansetron group (38.82%) compared to the control group (56.98%) (p = 0.0174). A similar trend was observed for the 2 to 24-hour period, with the ondansetron group exhibiting a significantly lower incidence of PONV (8.24%) than the control group (19.77%) (p = 0.0300). The mean VAS scores were also significantly lower in the Ondansetron group at both intervals (all p < 0.0001, Table 2). These findings suggested that ondansetron

Table 2 The Incidence and Severity of PONV at Different Time After Surgery in Control Group and Ondansetron Group

Variables	Control (N=86)	Ondansetron (N=85)	*p* Value
PONV incidence[a]			
First 2 hours	49 (56.98%)	33 (38.82%)	0.0174
2~24 hours	17 (19.77%)	7 (8.24%)	0.0300
VAS scores[b]			
First 2 hours	5.19 ± 0.82	2.42 ± 0.51	<0.0001
2~24 hours	2.76 ± 0.38	0.98 ± 0.25	<0.0001

Notes: [a]Values were presented as N (%); [b]Values were presented as Mean ± SD.
Abbreviations: PONV, postoperative nausea and vomiting; VAS, Visual Analog Scale.

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significantly reduced both the incidence and severity of PONV in patients undergoing laparoscopic gynecological surgery.

Frequency of Genotypes of OPRM1 A118G in the Control Group and the Ondansetron Group

To ensure comparability between cohorts, the distribution of OPRM1 A118G genotypes was analyzed in both the control and ondansetron groups (Table 3). In the control group, 43 patients (50.00%) exhibited the AA genotype, 30 patients (34.88%) had the AG genotype, and 13 patients (15.12%) carried the GG genotype. In the ondansetron group, 39 patients (45.88%) were homozygous for the AA genotype, 29 patients (34.12%) were heterozygous (AG), and 17 patients (20.00%) carried the GG genotype. Comparisons of genotype distributions between the two groups were performed using Pearson's chi-square test, and no significant differences were observed for either the AG (p = 0.866) or GG (p = 0.523) genotypes relative to the AA reference. These results confirm that the OPRM1 A118G genotype frequencies were comparable between the control and ondansetron groups, indicating adequate baseline genetic balance prior to efficacy analyses.

Presence and the Incidence of PONV at Different Times After Surgery in Various OPRM1 A118G Genotypes in the Control Group

The association between the OPRM1 A118G polymorphism and the incidence of PONV was investigated. The PONV incidence at various time intervals following surgery was shown in Table 4, stratified by OPRM1 A118G genotypes in the control group. The analysis revealed a significant correlation between OPRM1 A118G genotypes and PONV occurrence within the first 2 hours postoperatively ($p = 0.0009$). Specifically, 37.21% of patients with the AA genotype, 80.00% with the AG genotype, and 69.23% with the GG genotype developed PONV. However, no significant association was observed between 2 and 24 hours ($p = 0.2453$). In contrast, when the cumulative incidence of PONV over the 0 ~ 24-hour period was assessed, a significant association with the OPRM1 A118G genotype was found ($p = 0.0091$), with 62.79% of patients with the AA genotype, 90.00% of those with the AG genotype, and 92.31% of those with the GG

Table 3 Frequency of Genotypes of OPRM1 A118G in Control Group and Ondansetron Group

A118G genotypes[a]	Control (N=86)	Ondansetron (N=85)	OR value (95% CI)	*p* Value
AA	43 (50.00%)	39 (45.88%)	Ref	Ref
AG	30 (34.88%)	29 (34.12%)	1.07 (0.56 to 2.03)	0.8660
GG	13 (15.12%)	17 (20.00%)	1.44 (0.63 to 3.49)	0.5225

Notes: [a]Values were presented as N (%).
Abbreviations: OR, odds ratio; CI, confidence interval; Ref, reference.

Table 4 Presence and the Incidence of PONV at Different Time After Surgery in Various OPRM1 A118G Genotypes in Control Group

Variables	AA (N=43)	AG (N=30)	GG (N=13)	*p* Value (RAW)	*p* Value (Bonferroni)
PONV incidence[a]					
First 2 hours	16 (37.21%)	24 (80.00%)	9 (69.23%)	0.0009	0.0027
2~24 hours	11 (25.58%)	3 (10.00%)	3 (23.08%)	0.2453	0.7359
0~24 hours	27 (62.79%)	27 (90.00%)	12 (92.31%)	0.0091	0.0273

Notes: [a]Values were presented as N (%). Chi-square test was performed for overall comparisons among the three genotypes. Raw *p*-values were adjusted using Bonferroni correction.
Abbreviation: PONV, postoperative nausea and vomiting.

Table 5 Presence and the Incidence of PONV at Different Time After Surgery in Various OPRM1 A118G Genotypes in Ondansetron Group

Variables	AA (N=39)	AG (N=29)	GG (N=17)	*p* Value (RAW)	*p* Value (Bonferroni)
PONV incidence[a]					
First 2 hours	10 (25.64%)	16 (55.17%)	7 (41.18%)	0.0460	0.1380
2~24 hours	4 (10.26%)	2 (6.90%)	1 (5.88%)	0.8170	1.0000
0~24 hours	14 (35.90%)	18 (62.07%)	8 (47.06%)	0.1016	0.3048

Notes: [a]Values were presented as N (%). Chi-square test was performed for overall comparisons among the three genotypes. Raw *p*-values were adjusted using Bonferroni correction.
Abbreviation: PONV, postoperative nausea and vomiting.

genotype experiencing PONV. To account for multiple comparisons across time points, raw p-values were adjusted using the Bonferroni method for controlling the false discovery rate, and the corrected analysis results confirmed that our initial main findings were robust. These findings suggested that the OPRM1 A118G polymorphism was significantly associated with the occurrence of PONV, particularly in the early postoperative period.

Presence and the Incidence of PONV at Different Times After Surgery in Various OPRM1 A118G Genotypes in the Ondansetron Group

Subsequently, the incidence of PONV at various time intervals following surgery in the ondansetron group was compared in Table 5, stratified by OPRM1 A118G genotypes. A significant association was observed between the OPRM1 A118G genotypes and the occurrence of PONV within the first 2 hours postoperatively ($p = 0.0460$). Specifically, 25.64% of patients with the AA genotype, 55.17% with the AG genotype, and 41.18% with the GG genotype experienced PONV. However, no significant differences were observed between genotypes regarding the incidence of PONV from 2 to 24 hours post-surgery ($p = 0.8170$). Additionally, no significant association was found between the OPRM1 A118G genotypes and the cumulative incidence of PONV over the 0 ~ 24 hour period ($p = 0.1016$), with 35.90% of AA genotype patients, 62.07% of AG genotype patients, and 47.06% of GG genotype patients reporting PONV. To account for multiple comparisons across the three time points, raw p-values were adjusted using the Bonferroni method for false discovery rate control, and the corrected analysis results confirmed that none of the comparisons remained statistically significant after adjustment. These findings suggested that the OPRM1 A118G polymorphism was not associated with the occurrence of PONV in the ondansetron group.

The Incidence of PONV in the First Two hours After Surgery in Various OPRM1 A118G Genotypes in Two Groups

The incidence of PONV within the first two hours after surgery was compared, stratified by OPRM1 A118G genotypes (AA, AG, and GG) in both the control and Ondansetron groups. In the control group, the incidence of PONV was significantly higher in patients with the AG and GG genotypes compared to those with the AA genotype, with 37.21% of AA, 55.17% of AG, and 59.23% of GG genotype patients experiencing PONV (Figure 2). In contrast, a significant reduction in PONV incidence was observed in the ondansetron group across all genotypes (Figure 2). Specifically, 25.64% of AA, 55.17% of AG, and 41.18% of GG genotype patients in the ondansetron group developed PONV (Figure 2). These findings indicated that the OPRM1 A118G polymorphism, particularly the presence of the G allele, was associated with an increased risk of PONV, and that the ondansetron treatment was effective in mitigating this risk, especially in patients with higher genetic susceptibility.

Discussion

The application of SNPs for diagnosing PONV offers a significant advantage in identifying genetic susceptibility, facilitating precise risk stratification, and personalized therapeutic interventions. In contrast to traditional clinical risk factors, SNP analysis accounts for genetic variability, thereby elucidating discrepancies in PONV incidence among

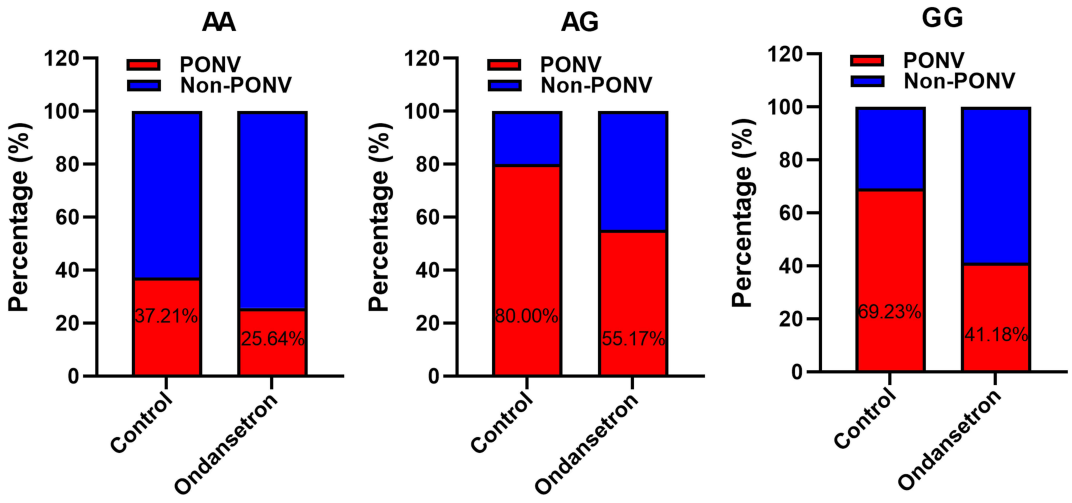

Figure 2 The incidence of PONV in the first two hours after surgery in various OPRM1 A118G genotypes in the control group and the ondansetron group. A118G genotypes, including AA, AG, and GG.
Abbreviations: PONV, patients with postoperative nausea and vomiting; Non-PONV, patients without postoperative nausea and vomiting.

patients with similar clinical characteristics. Furthermore, SNP profiling can inform the selection of antiemetic therapies, as specific genotypes may modulate drug efficacy, optimizing treatment outcomes. Our findings demonstrated that the OPRM1 A118G polymorphism was significantly associated with the incidence of PONV, particularly in the early postoperative period. Patients carrying the AG and GG genotypes exhibited a higher risk of PONV within the first 2 hours following surgery, suggesting that genetic variability plays a role in PONV susceptibility. Furthermore, ondansetron was effective in reducing the incidence and severity of PONV across all genotypes, particularly in patients with higher genetic susceptibility, such as those with the AG and GG genotypes.

The clinical baseline characteristics of the study cohort showed good comparability between the groups in terms of age, BMI, ASA classification, disease distribution, and surgery-related parameters, consistent with several published studies. Other studies have emphasized the importance of baseline comparability to ensure valid analyses,[22,23] which was achieved in this study through stringent inclusion criteria. Notably, some studies reported baseline differences related to race or gender,[24,25] which were not addressed in this study's stratified analyses. Compared to the standardized difference threshold of > 0.1 used in other studies to indicate clinical significance,[26] the p-values in this study were well above this threshold, confirming stronger baseline balance.

Several studies have demonstrated that ondansetron significantly reduced the incidence and severity of PONV, which aligned with our findings of a reduction trend in PONV incidence at 0 ~ 2 hours and 2 ~ 24 hours.[18,27] It has been reported that a single dose of ondansetron provided comparable efficacy to ramosetron in preventing PONV within 24 hours postoperatively,[18] with VAS score improvement consistent with other studies assessing nausea severity.[28,29] However, differences in the time window of assessment and duration of effect were noted. Some studies have extended the evaluation period to 48 hours,[30] while this study restricted observation to a 24-hour postoperative period. Additionally, it has been reported that the combination of ondansetron and dexamethasone can further reduce the incidence of PONV to 12.5%,[20] superior to the single-agent effect observed in our study. Furthermore, some studies suggested that ondansetron's effect may diminish during the 2 ~ 6-hour postoperative period,[31] whereas our study demonstrated sustained efficacy from 2 to 24 hours.

The genotype frequencies of OPRM1 A118G in the control and ondansetron groups were different from those reported in other studies. For instance, in the Saudi population, the A118G polymorphism showed 79.03% for AA, 16.13% for AG, and 4.84% for GG,[14] whereas in the control group of this study, the frequencies were 50%, 34.88%, and 15.12%, respectively. This difference may be attributed to population heterogeneity. Additionally, the incidence of PONV within 2 hours postoperatively was significantly higher in patients with AG/GG genotypes compared to AA genotypes, consistent with findings[15] that the G allele may impair μ-opioid receptor glycosylation, reducing opioid analgesic effects

and increasing PONV risk.[16] Furthermore, other research indicated that patients with both the OPRM1 A118G and BDNF G196A polymorphisms showed poorer pain relief,[32] further supporting the role of the G allele in promoting postoperative adverse reactions.

Ondansetron significantly reduced the early incidence of PONV in patients with all genotypes, consistent with previous findings,[19] suggesting that combining ondansetron with dexamethasone could further reduce the risk of PONV. Other studies have also confirmed that preoperative administration of ondansetron effectively prevents PONV within 24 hours postoperatively in breast cancer patients.[33] These results collectively indicate that ondansetron had a consistent effect across patients with different genetic backgrounds. However, another study emphasized that the CYP2D6 metabolic phenotype, rather than the OPRM1 genotype, is a key factor influencing the efficacy of ondansetron.[34]

CYP2D6 polymorphisms influence the metabolism of opioids, such as codeine, morphine, and fentanyl, which are commonly used for postoperative pain management. Ultra-rapid metabolizers (UMs) metabolize opioids more quickly, leading to higher concentrations of active metabolites and an increased risk of opioid-induced side effects, including PONV. Conversely, poor metabolizers (PMs) may have reduced opioid efficacy, requiring higher doses for adequate pain relief, which could also increase the likelihood of PONV.[35,36] Additionally, the interaction between opioids and ondansetron, a 5-HT3 receptor antagonist, may be affected by CYP2D6 polymorphisms. In ultra-rapid metabolizers, higher opioid doses may reduce ondansetron's effectiveness due to overlapping effects on the vomiting center. Conversely, poor metabolizers might not achieve adequate pain control, complicating the clinical scenario.[2,37] These genetic interactions suggest that CYP2D6 polymorphisms could be an important factor influencing PONV risk and antiemetic efficacy. Future studies combining OPRM1 and CYP2D6 polymorphism analyses could optimize PONV prevention strategies, particularly in genetically susceptible individuals.[38] Pharmacogenetic testing for both OPRM1 and CYP2D6 could help personalize PONV treatment, improving efficacy and safety while reducing unnecessary opioid use.

Additionally, it was reported that no significant association was found between the OPRM1 A118G polymorphism and opioid-related adverse reactions.[39,40] These discrepancies may arise from differences in study design, as this study focused on early PONV within 2 hours postoperatively, whereas other studies assessed long-term adverse reactions. This study found that the OPRM1 A118G polymorphism was significantly associated with PONV only within 2 hours postoperatively, while the cumulative incidence within 24 hours did not show a statistically significant difference in the ondansetron group. In contrast, the combination of Aprepitant and ondansetron has been shown to continuously reduce the risk of PONV over 24 hours, suggesting that genetic sensitivity to different antiemetic drugs may vary depending on the time window.[20] Furthermore, the PONV risk in patients with preoperative anxiety was found to be unrelated to the efficacy of ondansetron, further indicating that non-genetic factors may obscure the gene-drug association in PONV.[41]

This study highlights the clinical implications of the OPRM1 A118G polymorphism in managing PONV in laparoscopic gynecological surgery. It revealed that patients with AG and GG genotypes had a higher risk of PONV, particularly in the first two hours after surgery. Genetic screening for OPRM1 A118G could help identify high-risk patients, enabling more personalized treatment. Ondansetron was effective in reducing PONV across all genotypes, with a greater impact on those with higher genetic susceptibility (AG and GG). These findings suggested that combining ondansetron with other agents like dexamethasone may further benefit high-risk patients. Ultimately, incorporating genetic testing into PONV management could enhance treatment strategies, improving patient outcomes and reducing complications.

Although OPRM1 A118G genotyping provides valuable predictive information for personalized PONV management, its clinical implementation should consider cost and feasibility. The cost of genotyping using PCR and sequencing methods typically ranges between USD 20–50 per sample, depending on the laboratory platform and throughput. This cost is relatively low compared with the overall perioperative care expenses and could be justified for patients at high risk of PONV or those with repeated postoperative emetic episodes. However, large-scale cost–benefit analyses are needed to determine whether routine OPRM1 genetic screening is economically viable in clinical anesthetic practice.

This study still has several limitations. First, the retrospective design limits the ability to establish causal relationships between the OPRM1 A118G polymorphism and PONV, as it relies on pre-existing data and may be subject to biases,

such as selection bias and incomplete data. Additionally, the inclusion of cohorts from different time periods may introduce temporal bias, which could affect the consistency of the findings over time. Furthermore, although the sample size is adequate for statistical analysis, it may not fully represent genetic variability across different populations, limiting the generalizability of the findings. For example, the small sample size in the subgroup sizes for GG genotype limits the statistical power to detect moderate effects. These results should be interpreted as preliminary, and further studies with larger cohorts and more diverse populations are needed to confirm these findings. Additionally, the study focused on a 24-hour postoperative period, which does not account for the long-term effects of ondansetron. Lastly, the study did not account for other potentially relevant polymorphisms (eg, CYP2D6) or perioperative interventions (eg, non-antiemetic medications), which may influence PONV outcomes. These factors should be considered in future research to minimize confounding. Future prospective studies involving larger, more heterogeneous cohorts and extended follow-up periods are required to validate and further investigate these findings.

Conclusion

In conclusion, OPRM1 A118G polymorphism is significantly associated with an increased risk of PONV, particularly within the first 2 hours following surgery. However, it is important to note that the findings are based on a 24-hour observation period, and the long-term effects of ondansetron were not assessed in this study. Ondansetron effectively mitigated PONV across all genotypes, with enhanced efficacy observed in patients with higher genetic susceptibility. Future studies incorporating pharmacogenetic testing, particularly OPRM1 and CYP2D6 polymorphisms, may help optimize PONV prevention strategies.

Data Sharing Statement

Data are available on reasonable request.

Ethical Approval

The study was approved by Shandong Provincial Hospital Affiliated to Shandong First Medical University (#2025-03-207). Given the retrospective design and use of de-identified data, the requirement for individual informed consent was waived. The study was performed in strict accordance with the Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects.

Informed Consent

All patients signed the informed consent.

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Disclosure

The authors report no conflicts of interest int his work.

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