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ORIGINAL RESEARCH

Genetic Factors Associated with Morphine Consumption in Women Undergoing Laparoscopic Cholecystectomy: A Prospective Cohort Study

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Introduction: Morphine has been a crucial analgesic agent used perioperatively in various surgical procedures. Genetic factors can lead to morphine dose requirement interpatient variability. Our objective was to determine the contribution of genetic polymorphisms in human μ-opioid receptor gene (OPRM1), ATP binding cassette gene (ABCB1) and rs2952768 to the variation of the perioperative morphine consumption in women undergoing laparoscopic cholecystectomy.

Methods: This is a prospective cohort study that included 102 adult Arab females undergoing laparoscopic cholecystectomy. The exposures were carrying the genetic variants of *OPRM1, ABCB1* and rs2952768. Our primary outcome was total morphine or morphine equivalent dose required perioperatively. The secondary outcomes were pain score during the first 24 hours and adverse drug reactions. A standardized, general anaesthesia was used for all subjects. In addition to the genetic factors, we also investigated non-genetic factors influencing post-operative pain sensitivity and morphine consumption.

Results: Both (rs1799971, A>G) in *OPRM1* and (rs2952768, T>C) showed statistically significant association with intra-operative total morphine dose requirements. Patients carrying the "G" allele in *OPRM1* had a significantly higher total morphine mean rank dose compared to the AA genotype [62.9 vs 47.1, p=0.008]. Furthermore, patients homozygous for the rs2952768 (T>C) minor allele "CC" had a higher mean rank compared to the other genotypes [72.7 vs 50.1, p=0.046].

Conclusion: *OPRM1* (rs1799971) and rs2952768 are associated with variation of intra-operative morphine consumption in laparoscopic cholecystectomy.

Clinical Trial Identifier: This study was registered at ClinicalTrials.gov, NCT04621864. https://clinicaltrials.gov/ct2/show/NCT04621864.

Keywords: opioid, OPRM1, ABCB1, genetic polymorphisms, post-operative pain, women, Arabs

Introduction

For decades, morphine has been a crucial analgesic agent used in various clinical settings including periprocedural analgesic management. It induces its effects through the μ-opioid receptor (MOR). Clinical analgesic response to morphine varies from patient to patient leading to morphine dose requirement interpatient variability. Such variations have been owed to several factors including genetic polymorphisms in multiple genes. Among those is the*OPRM1* gene which encodes the human MOR.[1] *OPRM1* plays a major role in mediating the effects of opioids through both endogenous opioid peptides and exogenous ligands.[2] One of the most common single nucleotide polymorphisms (SNP) in the *OPRM1* gene is (rs1799971) which involves a substitution on nucleotide 118 A/G on exon 1 leading to an amino acid change from Asparagine to Aspartic acid. This SNP leads to an enhanced binding affinity of β-endorphin at MOR, which ultimately leads to increased potency at the receptor.[3,4] Additionally, variants in the ATP-binding cassette

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sub-family B member-1 (*ABCB1*) gene which codes for P-glycoprotein could influence morphine analgesic activity by affecting its absorption from the intestine and its transport via the blood–brain barrier.[5] Among other important SNPs shown to be associated with analgesic dose requirement is the rs2952768, which is an intergenic SNP located near the Methyltransferase Like 21A (*METTL21A*) gene. There has been numerous amount of variants that studied morphine clinical variability and it would be extremely difficult to test them all in this research. Based on our review, these 3 SNPs were among the most well-studied variants that showed some consistency in their effect on morphine outcomes.[5,6]

Our group has observed clinical variations in analgesic requirements among Arab patients. Only few reports have previously investigated the analgesic inter-individual variability in the Middle Eastern ethnicity. Most of them have focused on the influence of genetic variants on morphine dose requirements in cancer care and opioid dependence cohorts.[7–9] To our knowledge, no previous studies have evaluated the influence of morphine genetic polymorphism in the perioperative setting after laparoscopic cholecystectomy in Arabs. Therefore, we decided in this study to investigate whether the genetic polymorphism of human μ-opioid receptor gene (*OPRM1*), ATP binding cassette gene (*ABCB1*) and *rs2952768* are contributing to the variation of intra-operative morphine consumption in Arab women undergoing laparoscopic cholecystectomy. We decided to include only women in the study to eliminate the gender confounding effect on pain threshold and analgesic requirements. In addition to studying the association between genetic and non-genetic factors on the total perioperative morphine dose, we also assessed the effect of these factors on pain score, analgesic dosage requirements, and complications of morphine use in these patients during the first post-operative day as a secondary objective.

Methods

Research Design and Ethics

This was a prospective observational cohort study targeting Arab female adults undergoing laparoscopic cholecystectomy. Prior to the initiation of patient enrolment, the study was approved by the Qatar University's Institutional Review Board (QU-IRB 1297-FBA/20) and Hamad Medical Corporation's IRB (MRC# 01-18-270). Written informed consent was obtained from all subjects participating in the trial. The trial was registered at ClinicalTrials.gov (NCT04621864). The study complies with the Declaration of Helsinki.

Study Setting and Timeline

Patients were recruited at the anaesthesia clinic, Al Wakra Hospital, Hamad Medical Corporation (HMC), Qatar prior to their surgery. Recruitment started on October 20, 2019, and held during COVID-19 pandemic, and was completed on March 30, 2021. DNA samples were processed and analysed at the College of Pharmacy, Qatar University (QU), between August 2020 and April 2021.

Study Population and Sampling

The flowchart for inclusion, follow-up, and genetic analysis is shown in Figure 1. A total of 102 adult female patients with American Society of Anaesthesiologists physical status of I or II (class III cases were included if obesity is the only criteria) and in whom planned post-operative pain management by morphine was requested after laparoscopic cholecystectomy were included in this study. Patients were considered eligible if they were female Arabs (being of any of the League of the Arab States), above 18 years old, undergoing a laparoscopic cholecystectomy and agreed to participate in the study and signed an informed consent form. Patients were excluded if they had any obvious signs or symptoms of respiratory distress, cardiovascular disease, renal impairment, abnormal liver function with Child–Pugh classification other than A, were uncontrolled diabetics, had a history of allergy to morphine or experienced major side effects to morphine. Patients were also excluded if they had chronic pain that required long-term treatment with psychotropic or opioid medications. For the Arab ethnicity criterion, patients reported their nationality verbally, and it was confirmed through the patient's electronic health record (EHR).

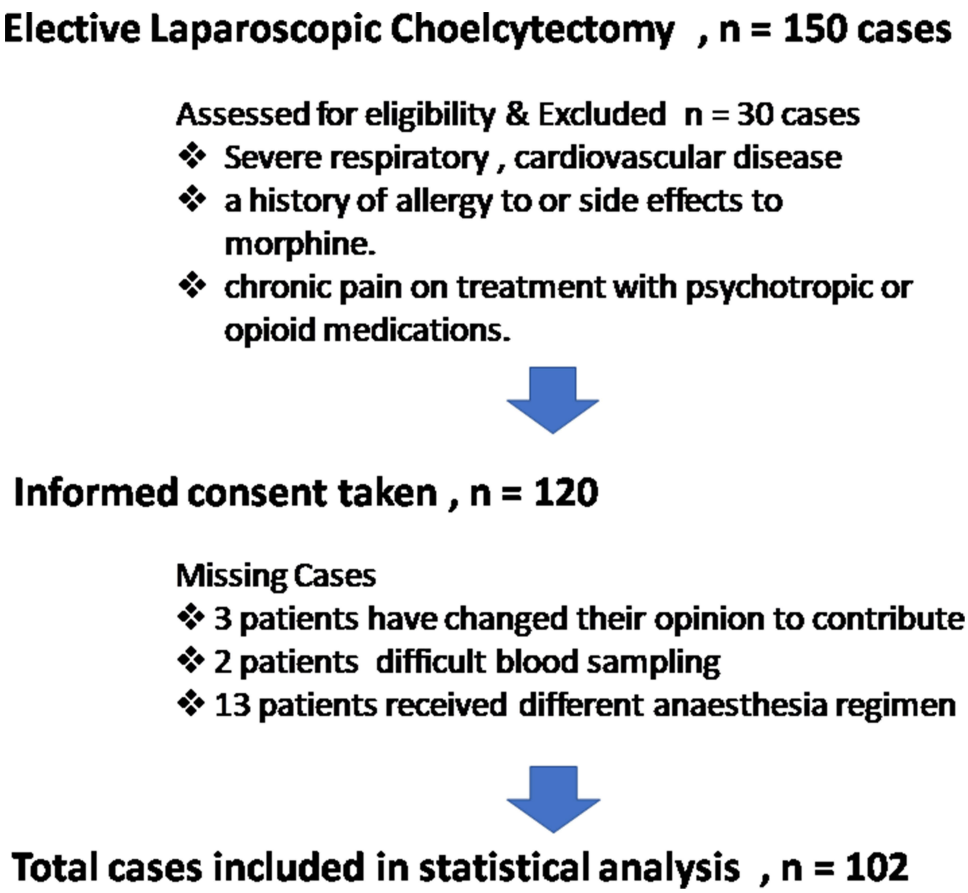

Figure 1 The flowchart for inclusion, follow-up and genetic analysis.

Data Collection and Outcome Measures

The primary outcome of this study was total morphine or morphine equivalent dose required during the surgery. The total equivalent intra-operative (IO) morphine dose was calculated as below:

$$Total\ equivalent\ morphine\ dose\ (mg) = IO\ fentanyl\ dose\ (mg) * 100 + morphine\ dose\ (mg)$$

The secondary outcomes were pain score during the first 24 hours using a Visual Analogue Score (VAS) and adverse drug reactions such as nausea, vomiting or respiratory depression. Main exposure was carrying genetic variants in *OPRM1, ABCB1, rs2952768*. Covariate factors such as age, comorbidities and BMI were also tested for their effect on the primary outcome (total equivalent IO morphine dose). After signing a written informed consent form, patients were asked to provide a blood sample. Blood samples were collected prior to surgery by the anaesthesiologist/anaesthesia technologist administering anaesthesia using BD Vacutainer® K3 EDTA 12.15 mg (15% Sol, 0.081 mL) plastic collection tubes (REF368861). Genetic laboratory tests were paid by the study.

Clinical data and demographics of the patients were collected primarily from the medical records and included: weight, height, BMI, age, patient past medical history, current medications, duration of surgery, duration of anaesthesia, dosages of anaesthetics using IO as standard anaesthesia protocol, total morphine administered IO and post-operative, other analgesic dosages (either intra-operative or post-operative), multimodal analgesia protocol in our institute, first time for rescue analgesics and post-operative possible complications of opioids (nausea, vomiting, itching, hypotension or respiratory depression). Pain-scoring using the Visual Analog Scale (VAS) was also documented.

Anaesthesia and Procedure Protocol

A standardized, general anaesthesia protocol was used for all patients. For induction of anaesthesia, 2 μg/kg fentanyl, 2 mg/kg propofol and 0.15 mg/kg cisatracurium were used. After induction of anaesthesia, cisatracurium and the inhaled anaesthetic sevoflurane at a low flow rate of 0.5 L/min were used to maintain the anaesthesia. Thirty minutes before the end of surgery, a 0.08 mg/kg loading dose of morphine was given intravenously (IV) and titrated by adding 2–3 mg as needed. At the end of the procedure, residual neuromuscular block was antagonized with neostigmine in 0.05 mg/kg and glycopyrrolate in 0.01 mg/kg, and patients were extubated. Post-operative nausea and vomiting (PONV) prophylaxis was given as part of our protocol, IV ondansetron, and IV dexamethasone intra-operatively.

After tracheal extubation, patients were transferred to the post anaesthesia care unit (PACU). Patients were assessed for pain score by anaesthetists on charge in PACU; by assessing the VAS score every 10–15 min after arrival in the PACU. Whenever the pain score increased to more than 3, incremental IV morphine titration was administered every 5 min in 2–3 mg IV increments until pain relief (VAS $\leq$ 3). All IV morphine doses were recorded. Study investigators did not intervene with the pain assessment, narcotic requirements, or ordering during the intra-operative or post-operative time; total administered analgesics during the post-operative 24-hour period were recorded and calculated. The respiratory rate and levels of consciousness were assessed at regular intervals. Average time for patient monitoring in PACU was one hour and then patients were discharged to the ward.

The modified Aldrete score is a widely used, objective method for evaluating post-anaesthetic patients. Each of the following measures received a score of 0, 1, or 2: activity (defined as moving all four limbs), respiratory efficiency, circulation (measured as arterial blood pressure at the pre-anaesthetic level), consciousness (defined as complete alertness), and oxygen saturation is maintained on room air or requires supplemental oxygen. The numbers assigned to each sign were added at the conclusion of each evaluation. In the best case scenario, a patient received a score of 10.[10]

In the surgical ward, a post-operative regimen was prescribed for rescue pain control as a standard of care: morphine 5 mg subcutaneous (SC) every 8 hours as needed (PRN); paracetamol 1 g IV every 6 hours PRN for nausea and vomiting; metoclopramide 10 mg IV every 8 hours PRN. These patients did not receive any type of regional blocks for pain management. One of our study's limitations was the implementation of multimodal analgesia utilizing paracetamol, non-steroidal anti-inflammatory (ketorolac), diclophenate and post-operative tramadol PRN as per institutional policy. Pain score was assessed in the ward every 6 h by a research team member.

Patients were monitored closely to prevent morphine overdose. Morphine adverse effects were reported nausea, vomiting, itching and respiratory depression. Respiratory rate (<10 breaths/min), arterial carbon dioxide level ($\geq$ 50 mmHg) and level of consciousness (progression to somnolence) were assessed at regular intervals. An IV infusion of 100–200 μg/h naloxone was started, to prevent morphine overmedication. When a patient requested treatment for nausea and/or pruritus concomitant with a VAS score greater than 8, naloxone was also administered to reverse the effect of morphine. All patients treated with naloxone because of the above-mentioned causes were excluded from the study analysis.

DNA Extraction, Quantification and Genotyping

Genomic DNA was extracted from fresh frozen whole blood samples using the PureLink® Genomic DNA mini kits, Invitrogen™, as previously described by our group.[11]

The Nanodrop 2000c Spectrophotometer (Thermo Fisher Scientific™) was used to quantify and assess the quality of the extracted DNA. For single nucleotide polymorphism (SNP) detection and genotyping, we used the QuantStudio™ 5 Real-Time PCR System for Human Identification, 96-well, 0.2 mL, desktop with TaqMan Drug Metabolizing Enzyme (DME) genotyping assay (Applied Biosystems™, Life Technologies). All probes were purchased at ThermoFisher Scientific; their context sequences are listed in Table S1.

Statistical Analysis and Sample Size Calculation

We planned to study 100 patients. We calculated the sample size as follows: if a genetic abnormality was found in 15% of patients and the average total morphine use in this subgroup was 40% lower/higher than in the remainder of

the patients, then we would have 80% power to detect that difference significantly with alpha error ≤ 0.05. Descriptive statistics and normality tests were used to analyse baseline demographics. Chi-square Goodness of Fit was used to make sure that all allele frequencies fit the Hardy–Weinberg Equilibrium (HWE). Since continuous variables were not normally distributed, we used non-parametric tests in most of our analysis. Mann–Whitney *U* or Kruskal–Wallis tests were used to estimate the difference in morphine requirements and difference in VAS score, when appropriate. Spearman's rho coefficient was used to test for association between total morphine dose and VAS score. The Chi-square test for independence was used to test for association between the patient's genotype and the need for post-operative morphine. Univariate regression analysis was used to estimate the effect of each genetic and clinical factor studied on total morphine dose. Furthermore, any factor with a *p*-value of 0.2 or below in the results of univariate analysis was tested in the multiple linear regression model. A two-tailed *P*-value <0.05 was considered significant. IBM Statistical Package for Social Science (IBM SPSS 27 software; IBM, New York, USA) was used to carry out the statistical analysis.

Results

Patient Recruitment and Study Population Characteristics

A total of 102 females undergoing laparoscopic cholecystectomy were recruited in the study. The majority of the patients were Qataris (49%) with a median (IQR) age of 38 (16) years and a median (IQR) weight of 77.5 (16.2) kg. About two thirds of the patients had an American Society of Anaesthesiologists physical (ASA) status of II. Table 1 shows detailed demographic data of the study subjects.

Table 1 Basic Characteristics of Patients Subjected to Laparoscopic Cholecystectomy

Demographic Data	Total (n=102)
Age, Median (IQR)	38 (16)
Height (cm), Median (IQR)	159 (8.3)
Weight (kg), Median (IQR)	77.5 (16.2)
BMI (kg/m^2), Median (IQR)	30.4 (6.8)
Nationality, n (%) **Qatari** **Egyptian** **Others**	 50 (49) 15 (14.7) 37 (36.3)
ASA, n (%) **I** **II** **III**	 27 (26.5) 67 (65.7) 8 (7.8)
Hypertension, n (%)	12 (11.8)
Respiratory, n (%)	16 (15.7)
Liver disease, n (%)	1 (1)
Diabetes, n (%)	13 (12.7)
Neurological, n (%)	0 (0)

Abbreviations: ASA, American Society of Anesthesiologists physical status; n, number; (%), percentage; IQR; interquartile range; BMI, body mass index; Others, Algerian, Jordanian, Kuwaiti, Lebanese, Moroccan, Palestinian, Sudanese, Syrian, Tunisian, Yemeni.

Intra-Operative and Post-Operative Information

On average, the surgery duration was one hour with a median of 65 (32) minutes and a median of 85 (35) minutes of anaesthesia. All intra-operative and post-operative data are represented in Tables 2 and S2 and show that four cases developed nausea and only two cases had vomiting.

Prevalence of *OPRM1* (A>G), *ABCB1* (G>A) and rs2952768

To estimate the prevalence of the studied genetic variants, we calculated their minor allele frequencies (MAF) in this cohort of Arab patients, and they were as follow: 0.15 for *OPRM1* (A>G); 0.38 for *ABCB1* (G>A); and 0.26 for rs2952768. Table S3 shows the MAF in comparison to other Arab nationalities. The genotype frequencies are shown in Table 3. No deviations from Hardy–Weinberg equilibrium were observed for any of the genotype frequencies.

Association of Genetic and Non-Genetic Factors with Total Intra-Operative Morphine Dose

Both *OPRM1 (rs1799971, A>G)*, and *rs2952768 (T>C)* showed statistically significant association with IO total morphine dose requirements. Patients carrying *OPRM1* minor allele (GG) and (AG) genotypes had a significantly higher total morphine mean rank compared to the AA genotype [62.9 vs 47.1, p=0.008] (Figure 2). Furthermore, patients homozygous for the *rs2952768 (T>C)* minor allele (CC) had a higher mean rank compared to the other genotypes [72.7 vs 50.1, p=0.046] (Figure 3). However, no significant association was found between the *ABCB1* genotypes and total IO morphine dose.

Multiple linear regression showed that weight, hypertension, using ketorolac during operation, carrying the *rs2952768* minor allele (CC) and carrying the *OPRM1* minor allele (GG) are all predictors of IO total morphine dose with an adjusted R^2 of 0.19 and a p-value less than 0.001 (Table 4).

Table 2 Intra-Operative Data of Patients Subjected to Laparoscopic Cholecystectomy

Intra-Operative Data	Total n=102
Surgery duration (minutes), Median (IQR)	65 (32)
Anesthesia (minutes), Median (IQR)	85 (35)
Fentanyl, n (%) Dose (μg), Median (IQR)	99 (97.1) 200 (0)
Ketorolac, n (%) Dose (mg), Median (Range)	81 (79.4) 30 (0)
Clonidine, n (%) Dose (μg), Median (Range)	13 (12.7) 0 (0)
Ketamine, n (%)	1 (1)
Paracetamol (1000 mg), n (%)	98 (96.1)
Morphine dose (mg), Median (IQR)	10 (5)
Metoclopramide (10 mg), n (%)	2 (2)
Ondansetron (4 or 8 mg), n (%)	98 (96.1)
Total morphine equivalent dose (mg)[a], Median (IQR)	30 (10)

Note: [aTotal] equivalent morphine dose=fentanyl dose (mg)×100+morphine dose (mg).
Abbreviations: n, number; (%), percentage; IQ, interquartile range.

Table 3 Genotype Frequencies of the Studied Genetic Variants

Genetic Variant	Genotype Frequencies, n (%) N=102	*P*-value for HWE
***OPRM1 (A>G)*, rs1799971**		
AA	74 (72.5)	0.62
AG	25 (24.5)	
GG	3 (2.9)	
***ABCB1 (G>A)*, rs1045642**		
GG	39 (38.2)	0.97
AG	48 (47.1)	
AA	15 (14.7)	
***METTL21A (T>C)*, rs2952768**		
TT	55 (53.9)	0.64
TC	41 (40.2)	
CC	6 (5.9)	

Abbreviations: *OPRM1*, human μ-opioid receptor gene; *ABCB1*, ATP binding cassette gene; METTL21A Gene, Methyltransferase 21A, HSPA Lysine.

Association of the Genetic Variants with VAS Score and Post-Operative Analgesic Requirements

There was no statistically significant association between *OPRM1* (rs1799971, A>G), rs2952768 (T>C) or ABCB1 (rs1045642, G>A) and the VAS score (overall and at each time point).

A significant correlation was found between post-operative morphine and VAS score at 0.5 and 1 hour (r=0.27, p=0.006 and r=0.24, p=0.015, respectively). The correlation was still significant when we considered the mean VAS score (r = 0.2, p=0.038).

Discussion

In this study, we attempted to investigate the effect of genetic polymorphism of *OPRM1, ABCB1* and rs2952768 on the variation of morphine consumption and pain score in women undergoing laparoscopic cholecystectomy. We observed

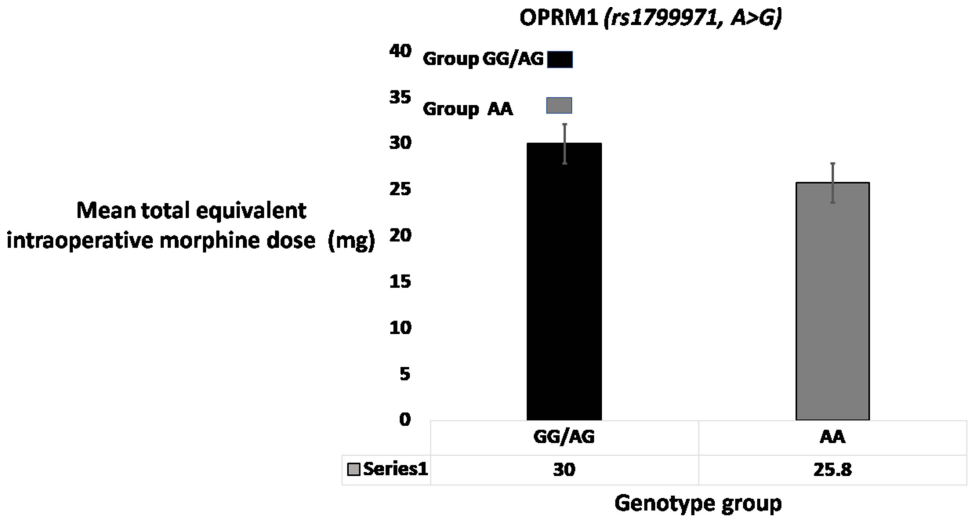

Figure 2 Effect of OPRM1 (A>G) genotypes on intra-operative equivalent morphine dose in women after laparoscopic cholecystectomy. Bar charts showing the difference in mean intra-operative morphine dose between OPRM1 genotype groups (GG/AG, n=28; AA, n=74). Although we used non-parametric tests (Mann–Whitney) to compare the difference in morphine requirements between groups, we reported the mean in this figure just to help visualize that difference. Since the median in both groups was the same and the interquartile range in one group equalled zero, we could not use box and whiskers to plot our results.

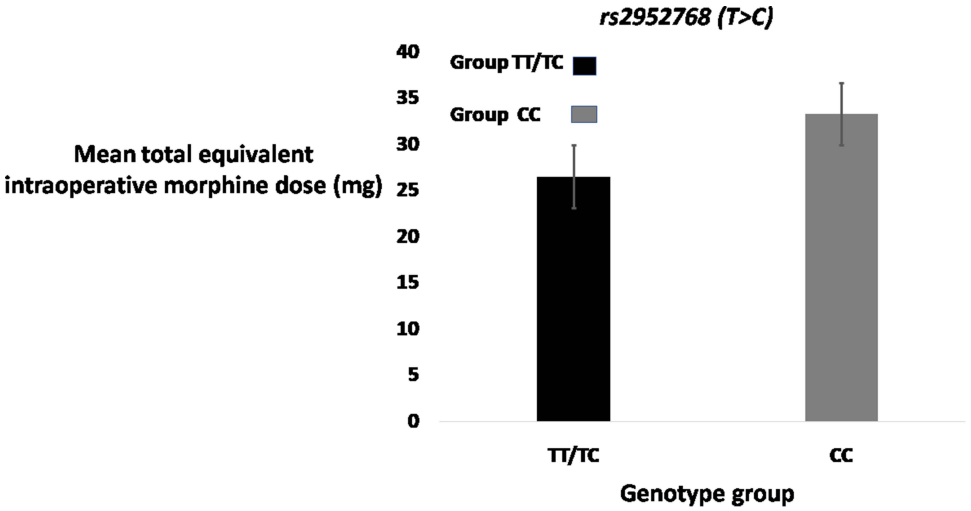

Figure 3 Effect of rs2952768 genotypes on intra-operative equivalent morphine dose in women after lap cholecystectomy. Bar charts showing the difference in mean intra-operative morphine dose between rs2952768 genotype groups (TT/TC, n= 96; CC, n=6). Although we used non-parametric tests (Mann–Whitney) to compare the difference in morphine requirements between groups, we reported the mean in this figure just to help visualize that difference.

that *OPRM1* (rs1799971, A>G) and the intergenic SNP-rs2952768 (T>C) are associated with IO total morphine dose requirements. This was confirmed in multiple linear regressions along with other clinical factors which included weight, use of ketorolac and ketamine during operation. However, there were no significant association with VAS score except for post-operative morphine use.

Genetic variability effect on the response to opioids for the treatment of pain post-surgery has been previously investigated.[12,13] Most of these studies have found that carriers of (*OPRM1* A118G) are more sensitive to pain. A Swedish study suggested a possible contribution of SNP within the *ABCB1* gene after laparoscopic cholecystectomy when comparing the pain sensitivity and post-operative pain intensity in a cohort of patients.[14] Regarding analgesic requirements, several studies have shown that carriers of *OPRM1* A118G require a higher dose of morphine in cancer and in different surgical settings. For instance, Klepstad et al found that patients with cancer usually require higher doses of morphine during their long-term therapy which was associated with the *OPRM1* 118G variant.[13]

In obstetric settings, Sia et al in 2008 demonstrated that A118G polymorphism was associated with inter-individual differences in IV morphine consumption post-operatively following a single intrathecal dose of morphine for post-operative analgesia after caesarean section.[15]

Table 4 Multiple Linear Regression Showing the Association of Genetic and Non-Genetic Factors with Intra-Operative Total Morphine Dose

Predictor	Coefficient B	Standard Error	*P*-value
Intercept	10.09	4.61	0.031
Weight	0.135	0.05	0.01
Hypertension	5.12	2.29	0.028
Ketorolac (Y/N)	3.54	1.86	0.06
rs2952768	2.94	1.1	0.009
OPRM1	4.45	1.32	0.001
Model Adjusted R^2=0.0143			<0.001

Abbreviations: (Y/N), yes OR no use of medication; OPRM1, human μ-opioid receptor gene.

A Japanese study[16] investigated fentanyl sensitivity and polymorphism in the *OPRM1* gene in a cohort of patients with painful orofacial surgery. Patients with the G allele of *OPRM1* were less sensitive to fentanyl and consumed more fentanyl post-operatively.[16] Similar fentanyl sensitivity study was conducted in Chinese gynaecology patients, where they concluded variation in intravenous fentanyl consumption and pain score in subjects with different *OPRM1* genotypes.[17]

rs2952768 (T>C) is an intergenic variant located between the *METTL21A* and *CREB1* genes. *rs2952768* and other neighbour SNPs included in that LD (linkage disequilibrium) block have been associated with post-operative opioid requirements in patients undergoing major abdominal surgery in a genome wide association study (GWAS).[6] Patients with CC genotype required significantly higher opioid dose compared to TT and T/C genotypes (t_{110}=−2.340, P=0.021). The same study tested the contribution of this SNP to the vulnerability to substance abuse. They observed fewer poly-drug abusers that are homozygous for the C variant compared to mono-drug users. Similarly, a group in Japan has attempted to construct a prediction formula for opioid analgesic requirement post surgery and they found that pain perception latency, weight and 4 SNPs (rs2952768; *OPRM1*A118G; *GIRK2*rs2835859; *ADRB2* rs11959113) are the significant predictors for 24-hour post-operative fentanyl requirement (R^2=0.145, P=5.66×10^{-10}).[18] Our study which was performed in laparoscopic cholecystectomy Arab female patients aligns with these previous findings.

Despite the high prevalence of *ABCB1* (G>A), rs1045642 variant, its association with opioid dose requirement has not been always consistent. A study on Italian patients showed that rs1045642 strongly affects morphine responsiveness and those patients homozygous for the *ABCB1* 3435T allele and the *OPRM1* 118A allele were the best responders to morphine.[19] Another research group from China found that patients managed on morphine for pain associated with undergoing a caesarean section and who were homozygous for the *ABCB1* 3435T allele tended to have persistent pain for three months after surgery compared to the CT and CC genotypes (P=0.07).[20] There were also previous reports that found an association between *ABCB1* variants and opioids adverse drug reactions such as fatigue and vomiting.[5]

Other than the association with the efficacy outcomes, we could not detect any adverse drug reaction within our studied sample. We also did not find any association between variants in *ABCB1* and morphine dose requirements.

Strengths

Our study is the first to investigate the association between genetic polymorphism and perioperative opioid consumption in the Middle East ethnicity. This study contributes new information to the field of genetic association and post-operative pain management after laparoscopic cholecystectomy. Few reports found *OPRM1* gene variants with susceptibility to opioid[9] and heroin[8] dependence, but there are no studies that discussed this association in the perioperative setting for this ethnic group. Therefore, our study could be a foundation for future research in this area. Moreover, the investigators performing all genotyping related experiments were blinded to the phenotypes, and all samples were managed and handled in a standard and systematic fashion to avoid any bias. Our study uses a critical approach to provide evidence of managing acute IO or perioperative pain and strengthens the future of personalized medicine.

Weaknesses

This study is not without limitation. First, there could be other genetic and non-genetic factors associated with morphine dose requirement that were not tested or collected. Second, our study sample size was small, yet we recruited all eligible patients undergoing laparoscopic cholecystectomy for a specified duration as a pilot study to explore the role of genetic polymorphism association with opioid consumption in our ethnic group. Additionally, intravenous patient-controlled analgesia infusion pumps were not available at our institution during the study period. Therefore, we used incremental IV morphine intra-operatively, in the PACU, continued with PRN SC morphine. Another limitation was the implementation of multimodal analgesia utilizing paracetamol, non-steroidal anti-inflammatory (ketorolac) and post-operative tramadol PRN as per institutional policy. Lastly, including female gender only in our study may have limited our generalizability. Further research could incorporate the addition of pharmacodynamic and pharmacokinetic genes: CYP2D6, CYP2C9, CYP3A4, CYP3A5 to identify male and female patients at risk for pain and other complications.

Conclusion

In this study, both *OPRM1* (rs1799971, A>G), and rs2952768 (T>C) showed a significant association with IO total morphine dose requirements in Arab female patients undergoing laparoscopic cholecystectomy. The same variants along with weight, having hypertension and using ketorolac remained as the main factors associated with total intra-operative morphine requirements.

Abbreviations

ABCB1, ATP binding cassette gene; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; OPRM1, human μ-opioid receptor gene; IRB, institutional review board; SD, 1 standard deviation.

Data Sharing Statement

The authors of this manuscript have no intention to share individual deidentified participant data.

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Disclosure

The authors declare no conflicts of interest.

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