RESEARCH PAPER

# Association of PONV and genotypes of 5ht3rb in Indian women undergoing surgery

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**Abstract**

Postoperative nausea and vomiting (PONV) are a common postoperative complication of patients under general anaesthesia despite antiemetic prophylaxis. Prevention and management of PONV involve administration of opioids analgesics, notably ondansetron, a selective 5-hydroxytryptamine 3 (5-HT3) receptor antagonist. Single nucleotide polymorphisms (SNPs) in relevant genes may influence receptor function or expression, contributing to inter individual variability in drug response. This study investigated the association between variants in the *HTR3B* gene and the risk of PONV. Women undergoing surgery under general anaesthesia received ondansetron as antiemetic prophylaxis. PONV was assessed every 6 hours over a 48 hours postoperative interval using standardized nausea and emesis scale. Peripheral blood was collected and genomic DNA was extracted. Genotyping was performed for *HTR3B* variants rs1176744 and rs3758987. The mean age of the participants was 39.47 ± 12.5 years, while height and weight were 153.42 ± 5.86 cm and 66.4 ± 11.83 kg, respectively. About 80% of participants reported nausea in the early postoperative period (0–6 hours), while severe vomiting episodes were rare and PONV scores gradually decreased over time. We observed a significant association between the rs1176744 AC genotype and reduced odds of PONV at 12–24 hours postoperative interval when compared with the AA genotype (OR = 0.16, 95% CI 0.02–0.77, p = 0.034). In contrast, rs3758987TT genotype showed a trend toward increased risk of PONV during the 6–12 hour postoperative period (OR = 3.18, 95% CI 0.93–10.9, p = 0.062), but this was not statistically significant. No consistent associations were observed at earlier postoperative intervals. The rs1176744 AC genotype may be a pharmacogenetic predictor for responsiveness to ondansetron for PONV. These findings support a potential role of genetic variation in the serotonergic pathway in modulating PONV susceptibility.

**Keywords:** Genotyping, *5HT3RB*, PONV, Ondansetron etc.

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## Introduction

Postoperative nausea and vomiting (PONV) is a common postoperative complication of patients under general anaesthesia despite antiemetic prophylaxis[1]. Postoperative bleeding, oesophageal rupture, hematoma, acid reflux and dehydration are some of other complications associated with PONV[2]. PONV occurs in about 30% of all surgeries[3]. Prevention and management of PONV has been primarily by use of opioids analgesics, and ondansetron, a selective 5-hydroxytryptamine 3 (5-HT3) receptor antagonist, is one such drug[4]. Serotonin (5-hydroxytryptamine, 5-HT) plays an important role in the emetic reflex pathway, where surgical stress can stimulate the release of 5-HT and cause vomiting reflex[5].Antagonists of the 5-HT3 receptors are thus widely used to treat and manage PONV[6]. Amongst the 5 subunits of 5HT3R, 5HT3RB is considered to play an important role in serotonin-receptor function[7]. Single nucleotide polymorphisms (SNPs) in the gene are known to influence gene expression and contribute to individual variations in the genetic profile[7]. Of the multiple variants of 5HT3RB, rs1176744and rs3758987 have been reported to be associated with incidence of PONV in various populations[7–10], however, studies in Indian population are limited. In this study, we investigated the association between HTR3B variants and PONV risk in South Indian women undergoing surgery under general anaesthesia who received antiemetic therapy.

## Material & Methods

Post-operative adult female patients who underwent surgery such as laparoscopic hysterectomy, cystectomy and cholecystectomy surgeries or mastoidectomy at Bangalore Baptist Hospital (BBH), Bengaluru, were asked to participate in the study. The study was conducted from February 2020 to March 2023. Patients not within the age of 20-60, under the medication of Cytochrome P450 inducers (e.g. Rifampicin, Phenobarbitone, Phenytoin) or inhibitors (e.g. Quinidine, Fluoxetine, Haloperidol),concomitant diseases that might cause nausea or vomiting (e.g., severe heart failure, ulcerations or obstructions of the upper gastrointestinal system, severe hepatic or renal dysfunction, and brain metastases),prolonged QT interval, motion sickness, pregnancy, active COVID-19 infection, or refusal to participate in the study were excluded.

The institutional ethics committees of BBH approved the study. Written informed consent was obtained before start of the study. All procedures were carried out in compliance with the ethical standards outlined in the Declaration of Helsinki. The study was conducted from February 2020 to March 2023.

According to Susan *et al*.[11], the percentage of PONV is anticipated to be 0.38. The necessary sample size for this investigation was 151, assuming a minimal odds ratio of 2 in poorly metabolized individuals with α and β errors of 1% and 20%, respectively, and power of 80%, 160 women were recruited in the study. Sample size was calculated using n Master 2.0 program (courtesy of the Biostatistics Resource & Training Centre at Christian Medical College, Vellore).

The day before their scheduled operation, participants underwent screening to determine if they met the study's requirements and written informed consent was obtained. Ranitidine 150mg H.S was given previous night of surgery and on the day of surgery preoperatively. All patients were given 0.1mg/kg ondansetron intra venously intra operatively. Assessment of PONV was done at 0-6, 6-12, 12-24 and 24-48 hours postoperatively using Nausea and Emesis Scale (Table 1).

**Table 1. Nausea and emesis scale.**

| Nausea and Vomiting Degree | Score |
|---|---|
| No nausea/retching and vomiting | 0 |
| Nausea/retching present, but no vomiting | 1 |
| Nausea/retching and vomiting present | 2 |
| Vomiting >2 episodes | 3 |

Patients were asked to rate their severity of nausea or vomiting by making a mark on theScale.If the patient vomited, they were given a rescue anti-emetics ondansetron 0.05mg/kg as step1, followed by Metoclopramide 0.15 mg/kg and Dexamethasone 0.1mg/kg i.v as step 2 and step3, respectively. Patients were categorised into 4 groups according to their surgical procedures (Table 2).

**Table 2. Categorization of patients according to their surgical procedure.**

| | |
|---|---|
| Groups 1 | Tympanoplasty, Mastoidectomy, Tympano mastoidectomy |
| Groups 2 | Breast Carcinoma, Breast Lumps, Modified Radical Mastectomy (MRM) |
| Groups 3 | Laparoscopic Cholecystectomy, Chole Lithiasis, Laparoscopic Hernia, Laparoscopic Appendectomy, Gall Bladder Polyp |
| Groups 4 | TLH, LAVH, Infertility, Ovarian Cystectomy, Tube Ligation, Family Planning, Myomectomy, Hysterectomy, Laparoscopic Cystectomy |

***DNA extraction:*** Post operatively 5 mL of intravenous blood was collected in EDTA tubes and transferred into an ice box until further processing. Whole blood was centrifuged and buffy coat was collected and stored at -80°C until analysis. DNA was extracted by TRI method following a modified manufacturer's protocol (Sigma-Aldrich Co. St. Louis, USA). Briefly, one-part buffy coat was mixed with four-parts TRI, and one chloroform (1:5, chloroform: TRI), and centrifuged at 12000 rcf for 15 min at 4°C.The aqueous layer was washed with chloroform to remove excess phenol. Chilled isopropanol and glycogen were used to pellet the DNA. The pellet was washed with chilled 75% ethanol and later dissolved in 22µLnuclease-free water. DNA was quantitated using Biotek Synergy H1 reader (Agilent Technologies, Inc., California, USA).

***Genotyping:*** *HTR3B* (rs1176744 and rs3758987) TaqMan SNP Genotyping assays were procured from Thermo Fisher (Thermo Fisher, Massachusetts, USA). The TaqMan assays are designed such that the dyes VIC and FAM correspond to only one variant each. A real-time qPCR reaction was performed according to the manufacturer's recommendations (Thermo Fisher, Massachusetts, USA). In brief, the reaction mixture contained 5 µL of Universal Master Mix (2x) (Thermo Fisher, Massachusetts, USA), 0.5µL of 40x *HTR3B* genotyping assay mix (Thermo Fisher, Massachusetts, USA), and 5.5µL of DNA (20ng) diluted in nuclease-free $H_2O$. The thermal cycling protocol consisted of an initial cycle for 10 min at 95°C, followed by 50 cycles at 92°C for 15 sec, and 60°C for 90 sec in Quant Studio

6 Flex (Applied Biosystems, Foster City, USA). Genotype calling was done using QS real-time PCR software (version 1.4.0.0, Applied Biosystems, Foster City, USA). A successful allele call was considered valid when either one or both florescence signal(s), corresponding to homozygous or heterozygous alleles, respectively, passed the threshold of the reference florescence signal. In cases where the software did not auto-assign the genotype, manual genotype was assigned based on the florescence intensity as homozygous or heterozygous. If the samples were not amplified, they were categorized as outliers and excluded from analyses. Hardy Weinberg equation was used to calculate the allele frequencies[12].

***Statistical Analysis:*** Continuous variables were assessed for distribution and are presented as mean ± standard deviation (SD) for normally distributed variables or median with inter quartile range (IQR) for non-normally distributed variables. Categorical variables are presented as counts and percentages. Chi-square tests or Wilcoxon rank sum tests or Fisher's exact tests were used for where appropriate. Associations between genetic variants and PONV were assessed using univariate logistic regression models. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated to estimate the strength of association between genotypes and PONV across different postoperative time intervals. Genotypes were analysed using categorical models with the most common genotype as the reference group. Separate analyses were performed for each postoperative interval (0–6, 6–12, 12–24, and 24–48 hours). $P<0.05$ was considered statistically significant.

**Results**

We analysed data from 159 participants. The mean age was 39.47 ± 12.5 years, height was 153.42 ± 5.86 cm, and body weight was 66.4 ± 11.83 kg. Participants were categorized into four clinical groups. Group 1 comprised 9 participants (5.66%), Group 225 participants (15.7%), Group 3 57 participants (35.9%), and Group 4 68 participants (42.8%). PONV occurrence was assessed at multiple postoperative intervals. During the 0–6 hour postoperative period 29 (20.9%) experienced PONV, while 110 (79.1%) did not report symptoms (n=139).In the 6–12 hour interval,33 (23.9%) reported PONV, whereas 105 (76.1%) remained symptom-free (n=138). In the 12–24 hour postoperative period, 14 (11.3%) experiencing PONV and 110 (88.7%) reporting no symptoms (n=124). In the 24–48 hour interval, 6 (7.8%) reported PONV, while 71 (92.2%) did not experience symptoms (n=77). Overall, the incidence of PONV declined progressively with increasing time after surgery (Table 3).

**Table 3. Clinical characteristics of the study participants.**

| Characteristic | n = 159[1] |
|---|---|
| Age (n=158) | 39.5±12.50 |
| Height (n=137) | 153.4±5.86 |
| Weight (n=153) | 66.4±11.83 |
| Diagnostic procedure Groups | |
| 1 | 9 (5.66%) |
| 2 | 25 (15.72%) |
| 3 | 57 (35.85%) |
| 4 | 68 (42.77%) |
| PONVat 6hrs | |
| 0 | 110 (79.14%) |
| 1 | 18 (12.95%) |
| 2 | 10 (7.19%) |
| 3 | 1 (0.72%) |
| PONVat 12hrs | |
| 0 | 105 (76.09%) |
| 1 | 25 (18.12%) |
| 2 | 5 (3.62%) |
| 3 | 3 (2.17%) |
| PONVat 24hrs | |
| 0 | 110 (88.71%) |
| 1 | 12 (9.68%) |
| 2 | 2 (1.61%) |
| PONVat 48hrs | |
| 0 | 71 (92.21%) |
| 1 | 4 (5.19%) |
| 2 | 1 (1.30%) |
| 3 | 1 (1.30%) |
| PONV.6hrs.new | |
| PONV Absent | 110 (79.14%) |
| PONV Present | 29 (20.86%) |
| PONV.12hrs.new | |
| PONV Absent | 105 (76.09%) |
| PONV Present | 33 (23.91%) |
| PONV.24hrs.new | |
| PONV Absent | 110 (88.71%) |
| PONV Present | 14 (11.29%) |
| PONV.48hrs.new | |
| PONV Absent | 71 (92.21%) |
| PONV Present | 6 (7.79%) |
| PONv.within.48.hrs | |
| PONV Absent | 42 (55.26%) |

| | |
|---|---|
| PONV Present | 34 (44.74%) |
| PONv.within.24.hrs | |
| PONV Absent | 78 (63.41%) |
| PONV Present | 45 (36.59%) |
| Allele frequency of rs1176744 | |
| AA | 44 (34.65%) |
| AC | 61 (48.03%) |
| CC | 22 (17.32%) |
| Allele frequency of rs3758987 | |
| CC | 55 (39.57%) |
| TC | 62 (44.60%) |
| TT | 22 (15.83%) |

[1]*Mean±SD; n (%)*

***Genotyping:*** Genotyping was performed using genomic DNA. The major allele in the population was considered as the 'reference allele' [13]. Two *HTR3B* SNPs, rs1176744 and rs3758987, were evaluated. Within rs1176744, AC genotype was the most frequent (61 individuals, 48.0%), followed by AA (44 individuals, 34.7%) and CC (22 individuals, 17.3%). For rs3758987, TC genotype was the most common (62 individuals, 44.6%), followed by CC (55 individuals, 39.6%) and TT (22 individuals, 15.8%). Hardy Weinberg equilibrium was calculated to be 1.

***Association of polymorphisms with PONV:*** Univariate logistic regression analysis was used to examine the association between *HTR3B* polymorphisms and PONV across different postoperative intervals (Tables 4-7). In rs1176744, the AC genotype was associated with a significantly lower odds of PONV during the 12–24 hour postoperative interval when compared with the AA genotype (OR = 0.16, 95% CI 0.02–0.77, p = 0.034) (Table 6). The CC genotype did not show a statistically significant association with PONV during the same interval (OR = 0.50, 95% CI 0.07–2.49, p = 0.40). In rs3758987, the TT genotype showed a trend toward increased risk of PONV during the 6–12 hour postoperative period (OR = 3.18, 95% CI 0.93–10.9, p = 0.062), but this was not statistically significant (Table 5). No statistically significant associations were observed for other genotype across the remaining postoperative intervals (Tables 4, 7).

**Table 4. Association of polymorphisms with PONV at 0-6 hours of postoperative interval.**

| Characteristic | N | OR[1] | 95% CI[1] | p-value |
|---|---|---|---|---|
| Age | 138 | 0.99 | 0.96, 1.02 | 0.5 |
| Height | 121 | 1.03 | 0.96, 1.11 | 0.4 |
| Weight | 137 | 1.01 | 0.97, 1.05 | 0.6 |
| rs1176744 | 112 | | | |
| AA | | — | — | |
| AC | | 2.21 | 0.77, 7.40 | 0.2 |
| CC | | 0.34 | 0.02, 2.36 | 0.3 |
| rs3758987 | 120 | | | |
| CC | | — | — | |
| TC | | 1.11 | 0.43, 2.92 | 0.8 |
| TT | | 0.45 | 0.06, 1.93 | 0.3 |

[1]OR = Odds Ratio, CI = Confidence Interval

**Table 5. Association of polymorphisms with PONV at 6-12 hours of postoperative interval.**

| Characteristic | N | OR[1] | 95% CI[1] | p-value |
|---|---|---|---|---|
| Age | 137 | 0.97 | 0.94, 1.01 | 0.11 |
| Height | 120 | 1.02 | 0.95, 1.09 | 0.6 |
| Weight | 136 | 1.02 | 0.99, 1.06 | 0.2 |
| rs1176744 | 111 | | | |
| AA | | — | — | |
| AC | | 0.93 | 0.34, 2.65 | 0.9 |
| CC | | 1.35 | 0.35, 4.88 | 0.7 |
| rs3758987 | 119 | | | |
| CC | | — | — | |
| TC | | 1.46 | 0.55, 4.09 | 0.5 |
| TT | | 3.18 | 0.93, 10.9 | 0.062 |

[1]OR = Odds Ratio, CI = Confidence Interval

**Table 6. Association of polymorphisms with PONV at 12-24 hours of postoperative interval.**

| Characteristic | N | OR[1] | 95% CI[1] | p-value |
|---|---|---|---|---|
| Age | 124 | 1.00 | 0.95, 1.04 | >0.9 |
| Height | 109 | 0.99 | 0.90, 1.09 | 0.8 |

| | | | | |
|---|---|---|---|---|
| Weight | 123 | 1.00 | 0.95, 1.04 | 0.8 |
| rs1176744 | 99 | | | |
| AA | | — | — | |
| AC | | 0.16 | 0.02, 0.77 | 0.034 |
| CC | | 0.50 | 0.07, 2.49 | 0.4 |
| rs3758987 | 106 | | | |
| CC | | — | — | |
| TC | | 0.65 | 0.15, 2.65 | 0.5 |
| TT | | 1.54 | 0.29, 7.18 | 0.6 |
| [1]OR = Odds Ratio, CI = Confidence Interval | | | | |

**Table 7. Association of polymorphisms with PONV at 24-48 hours of postoperative interval.**

| Characteristic | N | OR[1] | 95% CI[1] | p-value |
|---|---|---|---|---|
| Age | 77 | 1.00 | 0.93, 1.08 | >0.9 |
| Height | 66 | 0.90 | 0.77, 1.04 | 0.2 |
| Weight | 76 | 1.01 | 0.94, 1.08 | 0.8 |
| rs1176744 | 60 | | | |
| AA | | — | — | |
| AC | | 0.31 | 0.01, 3.46 | 0.4 |
| CC | | 1.00 | 0.04, 11.9 | >0.9 |
| rs3758987 | 69 | | | |
| CC | | — | — | |
| TC | | 1.00 | 0.11, 8.81 | >0.9 |
| TT | | 4.00 | 0.42, 38.6 | 0.2 |
| [1]OR = Odds Ratio, CI = Confidence Interval | | | | |

**Discussion**

We genotyped 159 south Indian women who underwent surgery for their various clinical complications and then were administered antiemetic drugs. About 80% of patients reported nausea in the early postoperative period (0–6 hours), while severe vomiting episodes were rare and PONV scores gradually decreased over time. Two variants of *HTR3B*, namely, rs1176744 and rs3758987, were investigated for their association with PONV. We observed a significant association between the rs1176744 AC genotype and reduced odds of PONV at 12–24 hours after surgery. In contrast, rs3758987 showed only a non-significant trend toward increased PONV risk. No consistent associations were observed at earlier postoperative intervals. These findings are important because PONV remains one of the most common and complications after anaesthesia and surgery. Our results suggests that genetic variation in the serotonergic pathway may influence not only whether PONV occurs, but also when it is most likely to occur.*HTR3B* gene encodes the B subunit of the 5-hydroxytryptamine type-3 (5-HT3) receptor[14]. The 5-HT3 receptor is a ligand-gated ion channel that mediates serotonin-induced signalling in both the central and peripheral nervous systems, and plays an important role in the emetic reflex pathway[14]. Variants in *HTR3B* have been reported to influence receptor function, including receptor kinetics and serotonin responsiveness[15]. Alterations in the receptor activity could therefore modify nausea and vomiting susceptibility by changing serotonergic neurotransmission in the gastrointestinal tract and brainstem emetic centres[16]. Although inconsistent, previous reports suggest that *HTR3B* polymorphisms may contribute to individual susceptibility to nausea and vomiting, and our reports suggests the same. Gloor *et al*. reported a modest but not statistically significant association between rs1176744 AC and PONV[5]. In Chinese Han women, no statistically significant association between rs1176744 and PONV was observed[7]. Laugsand *et al*. reported that participants with the rs1176744 GG genotype had less intense nausea[17]. Taken together, these studies suggest that the effect of *HTR3B* variation is present, it depends on the population, clinical conditions, antiemetics given, and genetic factors.

There are several limitations of our study. First is our relatively modest sample size of 159 patients. As PONV is a multifactorial condition that is influenced by demographic factors, anaesthetic agents, type of surgery and individual susceptibility, our findings are not generalizable. Although genetic variation may contribute to PONV risk, it likely interacts with multiple environmental and clinical factors. Finally, we investigated only two polymorphisms within the *HTR3B* gene, and other genetic variants in the serotonergic pathway may also play important roles in determining PONV risk. Despite these limitations, our study provides evidence supporting a protective role of *HTR3B* genetic variation in influencing PONV. Identification of more genetic variants associated with PONV susceptibility may ultimately contribute to

personalized postoperative care. Future studies with larger sample sizes, diverse populations and comprehensive genetic analyses are needed to confirm these findings and ultimately improve patient care.

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**Conflict of interest**

The authors have no conflicts of interest regarding this investigation.

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