American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 14, No 10 (October), 2013: pp 1045-1052
Available online at www.jpain.org and www.sciencedirect.com

Influence of Mu-Opioid Receptor Variant on Morphine Use and Self-Rated Pain Following Abdominal Hysterectomy

Alex T. Sia,*,† Yvonne Lim,* Eileen C. P. Lim,† Cecilia E. Ocampo,* Wai-Yee Lim,§ Philip Cheong,† and Ene-choo Tan†

**Department of Women's Anaesthesia, KK Women's and Children's Hospital, Singapore.*
†KK Research Centre, KK Women's and Children's Hospital, Singapore.
§Department of Maternal-Foetal Medicine, KK Women's and Children's Hospital, Singapore.

Abstract: A common variant in the mu-opioid receptor gene (*OPRM1*) has been associated with response to opioid analgesia. Our previous data revealed significantly higher amounts of morphine self-administered by patients carrying the 118G allele compared to those with the 118A allele after elective cesarean section. In this study, the association of this genetic variation with pressure pain, postoperative pain scores, and amount of morphine used was investigated in 973 patients undergoing scheduled total hysterectomy under general anesthesia. Preoperative pressure pain threshold and tolerance were also measured for most patients. For pressure pain, *OPRM1* genotype was not significantly associated with either pain threshold or pain tolerance. Statistically significant associations were found for postoperative pain and the total amount of morphine used, with the GG group reporting higher pain scores and using the most morphine. When analysis was stratified by ethnic group, differences in weight-adjusted morphine for the 3 genotypic groups were also significant for the Chinese and Asian Indians. These results extend our previous finding on the association of higher self-reported pain and morphine use for acute postoperative pain with *OPRM1* 118G to patients who had total hysterectomy under general anesthesia.

***Perspective:** In a large cohort of patients undergoing hysterectomy, we found large variability in the self-rated pain scores and the amount of morphine required for pain relief. Both are associated with* **OPRM1** *genotypes and preoperative experimental pressure pain threshold. Experimental pressure pain tolerance is also associated with postoperative pain.*

***Key words:** Hysterectomy, morphine,* OPRM1*, postoperative pain, pressure pain.*

Morphine delivered through patient-controlled analgesic pump (ie, patient-controlled analgesia [PCA]) is commonly given for the management of postoperative pain. If used correctly, it has the advantage of being instantly available without the need to request and wait for its administration, while ensuring that the patient gets only the amount needed at the proper time for pain relief.

Received October 6, 2012; Revised March 8, 2013; Accepted March 27, 2013.
This work was supported by grant no. NMRC/CPG/015/2005 from the National Medical Research Council, Ministry of Health, Republic of Singapore, and a project grant KRAU 108 from KK Women's and Children's Hospital.
There is no conflict of interest for any of the authors.
Address reprint requests to Ene-choo Tan, PhD, KK Research Centre, KK Women's and Children's Hospital, Singapore 229899. E-mail: tanec@bigfoot.com
1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2013.03.008

Because PCA morphine is based on patient demand and not standard dose, the actual amount used can be very different among individuals. There is a very wide range in the amount used by different patients in the same center even for the same type of surgical procedure.[11,22] As the amount of PCA morphine self-administered is based on individual need, this interindividual variability could be due to response to the therapeutic efficacy of morphine, apart from individual differences in pain sensitivity or tolerance.

As opioid analgesics act largely through the mu-opioid receptor, functional variants in the mu-opioid receptor gene are thus prime candidates accounting for the difference in the efficacy of morphine. Among the variants of the gene and receptor protein that have been associated with clinical effects of opioid analgesics in clinical populations, the variant producing the most consistent results is the nonsynonymous change from asparagine to aspartic acid at position 40 of the encoded protein (*OPRM1*

118A>G/N40D/rs1799971). In vitro and postmortem studies of human brains showed decreased expression, altered signaling efficacy, and lower mRNA expression compared to wild-type variants, whereas in vivo studies showed that the analgesic response to morphine-6-glucuronide was reduced in patients carrying the G genotype.[17,19,23,31] In clinical studies, carriers of the GG genotype also needed a higher dosage of morphine and were less responsive to the analgesic effect of morphine for cancer pain management.[2,25]

In a previous study with postcesarean patients, we found an association of the *OPRM1* 118A>G SNP (single nucleotide polymorphism) with self-reported pain and self-administered morphine in Chinese patients.[26] Another study with a small number of hysterectomy patients also found that patients carrying the GG genotype required more morphine.[3] To extend the results of the 2 studies, we investigated the effect of this polymorphism on self-rated postoperative pain and the amount of morphine self-administered for patients undergoing the same operation for the 3 main ethnic groups in our population.

Methods

Participants

This study involved a prospective cohort of women undergoing scheduled total hysterectomy under general anesthesia at KK Women's and Children's Hospital. All study procedures were approved by the hospital institutional review board. Subjects were recruited consecutively over 40 months from February 2006 to June 2009.

Study Procedure

Written informed consent was obtained from the patients after the study was explained to them before the scheduled procedure. Data were collected on age, weight, height, duration of operation, and postoperative vital signs. Subjects were asked to state their ethnicity and also that of their parents and all 4 grandparents. Only patients with the American Society of Anesthesiologists' physical status classification of 1 and 2 whose 4 grandparents were of the same ethnicity were included. Another criterion was absence of recreational drug use and history of long-term analgesic use.

Venous blood was collected at the time of obtaining written informed consent before surgery. Preoperative pain sensitivity and tolerance were assessed for patients by placing a size M (for arm circumference 23–33 cm) or L (for arm circumference 31–40 cm) blood pressure cuff of a sphygmomanometer on the upper arm of the patient as for noninvasive brachial blood pressure measurement. The cuff was then inflated. The pressure at which the patient first complained of pain and when the patient requested that the cuff be deflated were recorded as pain threshold and pain tolerance, respectively. For each patient, the average of 3 measurements was used.

General anesthesia was induced by using 1.5 mg/kg body weight (BW) of propofol and 2 μg/kg BW of fentanyl with .7 mg/kg BW of atracurium to facilitate tracheal intubation. Intraoperatively, intravenous (IV) morphine (.2 mg/kg BW) was given to supplement the maintenance of general anesthesia with sevoflurane and nitrous oxide. Antiemetics (ondansetron 4 mg and dexamethasone 4 mg) were given before the end of surgery.

Postoperative Pain Measures

At 4-hour intervals up to 24 hours of the immediate postoperative period (counting from the time of the arrival at the postoperative recovery area at the end of their surgery), subjects were asked to rate the degree of pain on the visual analog scale (VAS) consisting of 10 horizontal 10-mm scales, with 0 being "no pain at all" and 10 being "maximum pain." The pain scores were reported in integral numbers.

Morphine Use and Side Effects

All patients received an IV patient-controlled analgesic pump on arrival at the postoperative area. The PCA was set to deliver 1 mg IV bolus of morphine per demand with a lockout time of 5 minutes, without continuous background infusion. The maximum amount of morphine allowed was 10 mg/h. For the next 24 hours, the cumulative dose of morphine administered by each patient within every 4-hour period was recorded. Patients were monitored and could also request for additional IV morphine in 1-mg boluses.

Patients were also asked to rate nausea and pruritus on a severity scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe). Vomiting was recorded as the number of occurrences; and respiratory depression defined as a rate of <8 and/or shallow breathing.

Genetic Analysis

Venous blood was collected in ethylene diamine tetraacetic acid tubes. They were stored at −80°C and genomic DNA was extracted in batches from frozen whole blood samples using the Gentra Puregene Blood Kit (Gentra Systems Inc, Minneapolis, MN). DNA was checked for quantity and purity using the NanoDrop Spectrophotometer (NanoDrop Technologies, Wilmington, DE). The *OPRM1* 118A>G polymorphism was genotyped by the Taqman SNP Genotyping Assay (Applied Biosystems, Foster City, CA) as previously described.[27]

Data Analysis

Descriptive statistics were generated for demographic and clinical data and were compared between those who were included and excluded from analysis. Genotype distribution was assessed for Hardy-Weinberg equilibrium by means of chi-square tests. Summary statistics stratified by the 3 genotype groups of the *OPRM1* 118A>G were calculated for all variables using chi-square test for categorical variables and Student t-test or analysis of variance for continuous variables. The outcomes assessed were the following continuous variables: pain threshold,