

A118G Single Nucleotide Polymorphism of Human μ -Opioid Receptor Gene Influences Pain Perception and Patient-controlled Intravenous Morphine Consumption after Intrathecal Morphine for Postcesarean Analgesia

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Background: Previous studies have shown that genetic variability at position 118 of the human μ -opioid receptor gene altered patients' response to intravenous morphine. The purpose of this study was to investigate whether this polymorphism contributes to the variability in response to morphine for postcesarean analgesia.

Methods: After investigators obtained informed consent, 588 healthy women received 0.1 mg intrathecal morphine for postcesarean analgesia. Their blood samples were genotyped for the A118G polymorphism—A118 homozygous (AA), heterozygous (AG), or homozygous for the G allele (GG). Pain scores, the severity of nausea and vomiting, the incidence of pruritus, and the total self-administered intravenous morphine were recorded for the first 24 postoperative hours.

Results: Two hundred seventy women (46%) were AA, 234 (40%) were AG, and 82 (14%) were GG. The 24-h self-administered intravenous morphine consumption was lowest in the AA group ($P = 0.001$; mean, 5.9; 95% confidence interval, 5.1–6.8) versus the AG (8.0; 6.9–9.1) and GG groups (9.4; 7.3–11.5). Pain scores were lowest in the AA group and highest in the GG group, with a statistically significant difference detected between AA, AG, and GG ($P = 0.049$). Total morphine consumption was also influenced by patients' age and paying status. AA group was associated with the highest incidence of nausea (26 of 272 [9.6%]; $P = 0.02$) versus the other two groups (13 of 234 [5.6%] and 1 of 82 [1.2%] for AG and GG, respectively).

Conclusion: Genetic variation at position 118 of the μ -opioid receptor is associated with interindividual differences in pain scores, self-administered intravenous morphine, and the incidence of nausea postoperatively.

INTRATHECAL morphine, which predominantly exerts its effects through μ -opioid receptors, is widely used

for postcesarean analgesia. Several recent studies have suggested that polymorphisms of μ -opioid receptor gene (OPRM1) influence the efficacy of intravenous morphine.^{1,2} Specifically, the single nucleotide polymorphism (SNP) 118A>G (A to G substitution) in exon 1 of OPRM1, which results in the substitution of amino acid asparagine with aspartate at position 40, has been found to be associated with possible functional effects.^{3–6}

One *in vitro* study showed an increased affinity and potency of β -endorphin on homozygous G allelic receptor.³ However, a recent clinical study demonstrated that individuals homozygous for the wild-type A118 allele required less self-administered intravenous morphine to manage early posthysterectomy pain.⁷ Hence, the role of this polymorphism in influencing pain perception and analgesic requirement is controversial and not fully elucidated. In this cohort study, we investigated the effect of the A118G polymorphism of OPRM1 on the efficacy of a single dose of intrathecal morphine for postcesarean analgesia and the use of patient-controlled intravenous morphine in the first 24 h after surgery. To the best of our knowledge, there are no published studies that have investigated the effect of this polymorphism in postoperative pain management in pregnant women. We also investigated the propensity of the A118G polymorphism in causing side effects such as pruritus and nausea (and vomiting) in the perioperative obstetric patients.

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Materials and Methods

Patient Profile and Anesthetic Procedure

With the approval of the institutional review board of KK Women's and Children's Hospital, Singapore, and after obtaining written informed consent, we recruited into the study all American Society of Anesthesiologists physical status I, Chinese Singaporean women who presented for elective cesarean delivery at ≥ 37 weeks of gestation in the 18-month period from January 1, 2006, to June 30, 2007.

Only women who satisfied the following criteria were recruited:

1. Patients who self-reported that both natural parents and all grandparents were Singaporeans of Han Chinese descent

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2. Anthropometric profile within the following range: age 18–45 yr, weight 40–99 kg, and height 145–170 cm
3. Ability to comprehend and operate the patient-controlled analgesia (PCA) pump
4. Ability to comprehend and describe pain score by the 0–100 verbal/visual analog scales
5. Absence of history of drug dependence or recreational drug use

The exclusion criteria were as follows:

1. Presence of at least one medical condition, *e.g.*, hypertension or diabetes mellitus
2. Contraindication to spinal anesthesia and/or allergy to opioids or any of the drugs to be given intraoperatively

Baseline noninvasive blood pressure, heart rate, respiratory rate, and oxygen saturation by pulse oximetry were obtained before the initiation of anesthesia. On establishing the mandatory intravenous access before surgery, 3 ml blood was collected and stored. All the patients were given 0.5 l lactated Ringer's solution for prehydration before the induction of anesthesia.

Spinal anesthesia was induced with the patient in the right lateral position, and a 27-gauge Whitacre spinal needle was inserted at the L3–L4 level. When free flow of cerebrospinal fluid was established, 2 ml hyperbaric bupivacaine, 0.5% (Marcaïn; AstraZeneca, Sodertalje, Sweden), with 0.1 mg morphine was injected intrathecally. The women and attending anesthesiologists were blinded to the genotype at the time of surgery and throughout the clinical portion of the study because genotyping was determined only later. Surgery was initiated when sensory block to cold at patients' midline was detected at T4 level with the patients lying in the supine position with a 15° left lateral tilt. Hypotension (a reduction of systolic blood pressure of more than 20% of the baseline measured noninvasively on the same arm) was treated with 0.1-mg boluses of phenylephrine and intravenous crystalloids. Antiemetics (intravenous 4 mg ondansetron, 10 mg metoclopramide, and 4 mg dexamethasone) were routinely given before the end of surgery. The duration of surgery was recorded.

Cases were excluded if there was a failure to establish a free flow of cerebrospinal fluid after three attempts ("technical failure") or failure to establish a block of T4 after 30 min ("complete block failure"). In addition, cases with a partial block failure necessitating nitrous oxide by inhalation and/or intravenous fentanyl up to 100 µg were excluded from analysis because the use of intraoperative opioids and hypnotics could potentially affect pain scores and the use of PCA morphine postoperatively. Cases with complications such as hemorrhage necessitating additional procedures or surgery necessitating more than 120 min of operating time were also excluded from analysis.

Postoperative Management

After surgery, the time of arrival at recovery was defined as time 0. All of the patients were equipped with an intravenous PCA pump (Rhythmic, Micrel, Greece) set to the following regimen: bolus dose of 1 mg morphine, lockout of 5 min, and total hourly dose of 10 mg for treatment of postoperative pain. During the first 24 h postoperatively, no other supplemental analgesics were given.

Data related to patients' age, weight, height, body mass index, paying status (private *vs.* subsidized), history of previous cesarean delivery, duration of surgery, and pain scores at rest (0–10 visual analog scale) at time 0 were collected. Pain scores were recorded every 4 h after time 0, *i.e.*, at 4, 8, 12, 16, 20, and 24 h after time 0 for the first 24 h. PCA morphine was provided for pain relief and the total amount of PCA morphine over the first 24 postoperative hours was recorded; requests and boluses received served as a surrogate to the overall pain experience.

The following side effects were also recorded every 4 h after time 0, *i.e.*, at 4, 8, 12, 16, 20, and 24 h after time 0 for the first 24 h:

1. Nausea on a severity scale of 0–3: 0 = none, 1 = mild, 2 = moderate, 3 = severe
2. Vomiting as defined by the number of episodes of retching with or without expulsion of fluids from the stomach
3. Pruritus on a severity scale of 0–3: 0 = none, 1 = mild, 2 = moderate, 3 = severe
4. Central nervous system depression as defined by patients who were asleep and difficult to rouse with a moderately loud auditory stimulus (calling out patients' names) or glabellar tap
5. Respiratory depression as defined by a rate of less than 8 and/or shallow breathing and/or oxygen saturation of less than 90% on room air as indicated by pulse oximetry

Women with more than mild nausea and/or vomiting were treated with 10 mg intravenous metoclopramide and 4 mg intravenous ondansetron. Women with severe pruritus were offered 0.04–0.1 mg intravenous naloxone. Intravenous naloxone, 0.04–0.1 mg, and supplemental oxygen by mask were available for women with signs of central nervous system or respiratory system depression.

Laboratory Analysis

The blood specimens, which were collected at the time of intravenous cannulation before surgery, were analyzed for the presence of 118A>G SNP by using the following technique: Genomic DNA was extracted from 3 ml venous blood using the Genra Puregene Blood Kit (Genra Systems Inc., Minneapolis, MN). DNA was checked for quality and quantity using the NanoDrop

Spectrophotometer (NanoDrop Technologies, Wilmington, DE).

Genotyping for the A118G polymorphism (rs 1799971) was performed using the Taqman SNP Genotyping Assay ID C__8950074_1 (Applied Biosystems, Foster City, CA). Amplification was performed in a volume of 12 μ l containing 25 ng genomic DNA, Taqman Universal Polymerase Chain Reaction Master Mix, 60 nM of each probe, and 270 nM of each primer. Cycling and hybridization conditions were set according to manufacturer's instructions. The 50 cycles of denaturation and annealing/extension and post-polymerase chain reaction quantification of fluorescent intensity were performed using the Applied Biosystems 7300 Real-Time Polymerase Chain Reaction System.

Statistical Analysis

In this study, genotypes, *i.e.*, A118 homozygous (AA), A118 heterozygous (AG), and G118 homozygous (GG), were first treated as independent variables. The sample size of the study (588 subjects) has a power greater than 80% to detect an additive genetic effect corresponding to a 10% change in total morphine intake of the baseline genotype AA at a 5% level of significance.

Summary statistics were calculated for all the variables in each of the three genotypic groups. Numerical variables were assessed for the assumption of normality within each group with the Shapiro-Wilk test, and any variable that satisfied the assumption is summarized using the mean and SD. One-way analysis of variance was used to assess whether significant differences exist between the three genotypes for numerical variables that were normally distributed, whereas the Kruskal-Wallis rank sum test was used for numerical variables with skewed distributions. The Pearson chi-square test was used to investigate the extent of association between the genotypes and the categorical variables. The genotypes for the A118G polymorphism were tested for departures from Hardy-Weinberg equilibrium using a likelihood ratio test, and the call rate of the polymorphism was used as a surrogate for genotyping performance.

A two-way analysis of variance for repeated measures was used for pain scores and morphine consumption; the study groups (genotypes) were taken as between-subjects factor, and time (4–24 h after T0) was taken as repeated-measures factor. For the analysis of pruritus, nausea, and vomiting, the area under curve described by the severity scores was used to analyze the overall severity of these side effects over the whole duration of study.

Univariate analyses using the Wilcoxon rank sum test were performed to identify whether total morphine consumption differed between different levels of binary

categorical variables. A multivariate regression analysis together with a stepwise model-selection procedure using the Akaike information criterion was used to identify variables that explain total morphine consumption.⁸ Data were captured in the statistical program SPSS version 9.0 (Chicago, IL). The threshold of statistical significance was defined as 0.05, and all analyses were performed using the statistical software R.^{‡‡}

Results

A total of 631 women were enrolled; in 1 woman technical failure was encountered, 3 had complete block failure, and 32 had partial block failure. Seven cases developed intraoperative complications such as hemorrhage and required more than 120 min of operating time. Hence, only data from the remaining 588 women were analyzed in this study. Two hundred seventy-one (46%) were AA, 234 (40%) were AG, and 80 (14%) were GG. The call rate of genotyping was 99.5% (585 of 588). This sample size has a power greater than 80% to detect an additive genetic effect corresponding to a 10% change in total morphine intake of the baseline genotype AA at a 5% level of significance. The allelic frequencies for the A and G alleles were 66% and 34%, respectively. There were no significant differences in the demographic and baseline parameters of the three genotypic groups. There was also no difference in the duration of surgery among the groups (table 1).

There was a significant statistical difference in the total consumption of PCA morphine among the three groups ($P = 0.01$; table 1). When the serial 4-hourly consumption of PCA morphine was analyzed, there was a significant difference between the groups (fig. 1). All the groups showed a similar pattern of consumption, with the lowest mean doses used in the 12–16 h after time 0. There were no failed PCA demands throughout the study.

Pain scores recorded were low in all three groups, but the pain score was lowest in the AA group in the first 24 h postoperatively. There was also a significant difference in the total pain scores among the three groups ($P = 0.049$; table 1). When the serial 4-hourly pain scores were analyzed, there was a significant difference between the groups (fig. 2). Corresponding with the pattern of consumption of PCA morphine, pain scores were the lowest in the periods of 12 and 16 h after time 0, with the AA group recording the lowest scores.

The overall incidence of nausea was low; only 40 of the total 588 women (6.8%) had one or more episodes of nausea in the first 24 h postoperatively. The AA group was associated with the highest incidence (26 of 272 [9.6%]; $P = 0.02$) versus the other two groups (13 of 234 [5.6%] and 1 of 82 [1.2%] for AG and GG, respectively).

‡‡ R: A Language and Environment for Statistical Computing. Vienna, R Foundation for Statistical Computing. Available at: <http://www.R-project.org>. Accessed May 15, 2008.

Table 1. Demographic Data

	AA, n = 271	AG, n = 234	GG, n = 80	P Value
Age, yr	32.7 (4.6)	32.2 (4.7)	32.9 (4.9)	0.835
Weight, kg	69.0 (9.8)	69.6 (10.8)	68.5 (10.9)	0.959
Height, cm	158.5 (5.5)	157.9 (5.9)	159.0 (4.9)	0.899
BMI, kg/m ²	27.5 (3.7)	27.9 (4.0)	27.1 (4.0)	0.880
Paying class, private:subsidized	176:95	167:67	54:26	0.304
Prev C-sec, 0:≥1	92:179	97:137	24:56	0.1
Duration of surgery, min	52.5 (16.9)	52.2 (15.0)	54.1 (15.4)	0.730
Total morphine, mg	5.94 (7.36)	7.97 (8.47)	9.38 (9.36)	0.001*
Total VAS	2.83 (3.27)	3.49 (3.53)	3.73 (4.02)	0.049*

Data are expressed as mean (SD) unless otherwise indicated.

* Statistically significant difference found between the three groups.

AA = wild-type homozygous; AG = variant heterozygous; GG = variant homozygous; BMI = body mass index; Prev C-sec = history of previous cesarean delivery; VAS = 0–100 visual analog scale.

There was no statistical difference between the AG and GG groups. The AA group also experienced the highest severity scores for nausea over the first 24 h postoperatively from the analysis of the area under the curve for nausea scores ($P = 0.03$) versus the other two groups (table 2). There was no statistical difference between the AG and GG groups. The overall incidence of vomiting was low; only 32 of the total 588 patients (5.4%) had at least one episode of vomiting in the first 24 h postoperatively. There was no statistical difference in the proportions of patients who vomited at least once in the first 24 h postoperatively; the proportion of women who vomited at least once was 10 of 272 (4.3%) in the AA group versus 10 of 234 (4.3%) and 1 of 82 (1.2%) in the AG and GG groups, respectively ($P = 0.11$).

Two hundred seventy-four women (49%) developed pruritus. There was no statistical difference among the

groups; 136 of 272 (50%) in the AA group had pruritus versus 113 of 234 (48%) in the AG group versus 35 of 82 (43%) in the GG group ($P = 0.5$). There was no difference in the severity scores for pruritus over the first 24 h postoperatively (table 2). None of the women were treated with intravenous naloxone for this purpose. There was no case of respiratory or central nervous system depression, and no case withdrew from the study or was lost to follow-up.

The results of the multivariate regression model, together with a stepwise model-selection procedure using the Akaike information criterion to identify the variables that explain total morphine consumption, showed that age ($P < 0.05$) and payment class ($P < 0.0001$) of each subject contributed to total morphine intake, explaining 3.25% of the total variation observed in total morphine intake. Morphine consumption was less with increased age and in nonprivate patients. Correcting for age and

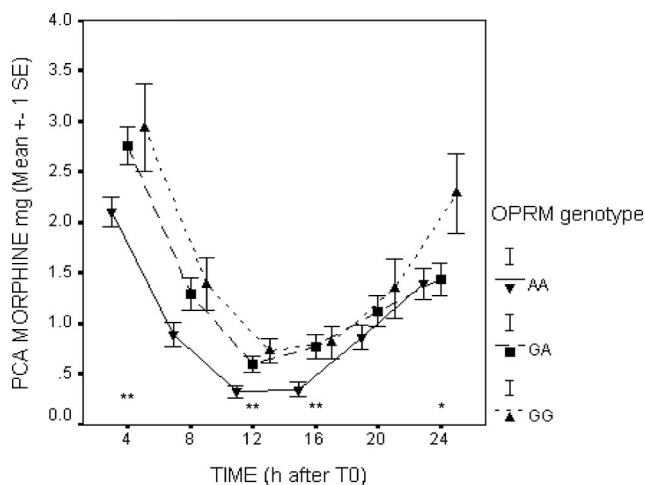


Fig. 1. Patient-controlled analgesia (PCA) morphine (mean \pm SE) consumption (milligrams) versus time (hours) after end of surgery (T0) for each genotype. ** Significant difference between wild-type homozygous (AA) and the other two groups ($P < 0.05$); no difference between variant heterozygous (AG) and variant homozygous (GG). * Significant difference between AA and GG ($P < 0.05$); no difference between AA and AG; no difference between AG and GG.

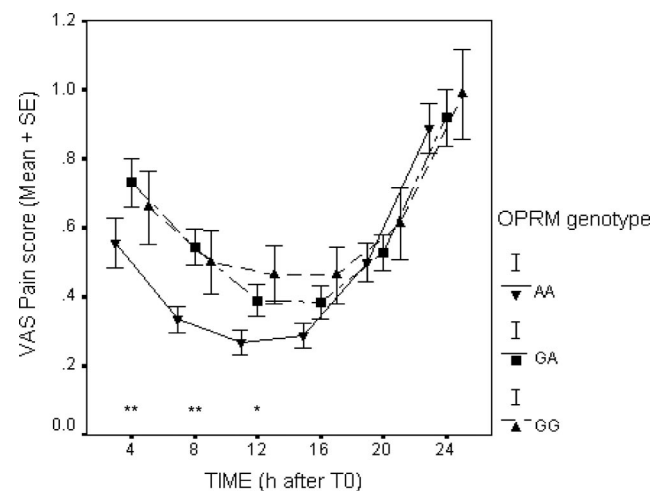


Fig. 2. Pain scores (mean \pm SE) versus time (hours) after end of surgery (T0) for each genotype. ** Significant difference between AA and the other two groups ($P < 0.05$), no difference between AG and GG. * Significant difference between wild-type homozygous (AA) and variant homozygous (GG) ($P < 0.05$); no difference between AA and variant heterozygous (AG); no difference between AG and GG. VAS = 0–100 visual analog scale.

Table 2. Side Effects

	AA, n = 272	AG, n = 234	GG, n = 82
Area under the curve for nausea scores over 24 h	0.02 (0–5)*	0.01 (0–2.5)	0.01 (0–0.83)
Area under the curve for pruritus scores over 24 h	0.42 (0–10)	0.01 (0–10)	0.01 (0–8.33)

Data are expressed as median (minimum–maximum).

* Significant difference between wild-type homozygous (AA) and the other two groups (variant heterozygous [AG] and variant homozygous [GG]; $P = 0.02$); no difference between AG and GG.

payment class, and under the assumption of an additive effects model, the genotypes of OPRM are found to significantly affect total morphine intake ($P < 0.0001$), with each additional copy of the G allele increasing total morphine intake by 1.87 mg (95% confidence interval, 0.95–2.79). The OPRM genotypes explain an additional 2.28% of the total variation in morphine consumption (5.52% for the model with OPRM genotypes *vs.* 3.25% for the model without OPRM genotypes).

Correcting for demographic parameters (age, height, and weight), duration of the operation, payment class, and incidence of previous cesarean delivery, the OPRM genotypes significantly explain the variation in pain scores ($P = 0.014$), with each additional copy of the G allele increasing pain scores (0–100 visual analog scale) by 0.51 units (95% confidence interval, 0.10–0.91). The OPRM genotypes explain an additional 0.98% of the total variation in pain scores (2.28% for the model with OPRM genotypes *vs.* 1.30% for the model without OPRM genotypes).

Discussion

The major finding of our study is that the A118G polymorphism of OPRM1 was associated with a significant variability in morphine consumption after intrathecal morphine for postcesarean analgesia. We demonstrated that women with the AA genotype consumed the least amount of PCA morphine and had demonstrably lower pain scores than the other genotypic groups. We infer that this could be due to a few factors, including a greater sensitivity of the AA group to the analgesic effect of intrathecal morphine that had reduced the need for supplemental opioids, a greater sensitivity to PCA morphine in counteracting postoperative pain in the AA group, or a combination of these factors. Although individual variability in the perception of postcesarean pain could be predicted by a multitude of factors, including responses to thermal sensitivity and anxiety questionnaire tests,⁹ there are hitherto no reports, to the best of our knowledge, that have investigated the effect of SNP A118G in postcesarean analgesic management. Our findings are consistent with previous clinical studies in the nonobstetric population that found patients with the AA genotype to be more sensitive to parenteral opioids than the GG variants in the postoperative clinical setting.^{2,7}

Similarly, the GG genotype has also been associated with a greater requirement for opioid analgesia in the management of malignant pain in another study.¹ Besides, our study also shows a “dose-dependent” effect of the G allele, with each additional copy increasing the total need for morphine. Our study is also strongly indicative that the advanced stage of pregnancy and its attendant physiologic changes do not alter the association of the genotype on this locus with pain perception and analgesic consumption.

The clinical impact of this particular μ -opioid receptor gene polymorphism remains controversial. An earlier *in vitro* functional study has demonstrated an enhanced binding affinity and potency of β -endorphin, an endogenous ligand, to the GG variant of the μ -opioid receptor, but this finding was not confirmed by other investigators.³ Although this may be apparently contradictory to our findings, the impact of the A118G polymorphism on functions such as alterations in gene expressions, transduction systems, or receptor trafficking remains to be determined.¹⁰ For example, the potential effect of repeated, enhanced binding of β -endorphin to the GG genotype on receptor desensitization, including receptor level alterations secondary to a down-regulated rate of receptor recycling, needs to be substantiated.¹¹ In addition to these physiologic changes, the contribution of the A118G polymorphism to behavioral and personality differences has also been suggested.¹² The importance of these factors regardless of their relation with the A118G polymorphism in determining the perception, experience, and effect of analgesics in the postoperative period would need further investigation.

The use of intrathecal morphine at the current dose has been found to be near optimal in a previous study.¹³ However, despite a similar dose of intrathecal morphine, the postcesarean parturients in the study of Palmer *et al.* consumed considerably more intravenous PCA morphine, *i.e.*, a mean of 26 mg but with an SD of 23 mg over the first 24 h postoperatively. We are unable to explain the discrepancy between the results of that study and ours, although it could be due to ethnic, environmental, or genetic differences between that study population and ours. In addition, our previous study showed that even without the benefit of intrathecal morphine, the mean consumption of PCA morphine was only approximately 14 mg (SD 2) over the first 24 h after cesarean

delivery (given that all patients had received 10 mg intravenous morphine intraoperatively).¹⁴

Our study also showed that individuals with the AA genotype had the highest risk of developing nausea, which was not associated with vomiting despite a lower consumption of PCA morphine. Hence, we could infer that the greater analgesic sensitivity to morphine accorded by the A allele is also related to a higher risk of developing nausea, although it is not apparent from this study whether this was predominantly due to neuraxial or parenteral morphine. The relation between postoperative nausea and intrathecal morphine is controversial. Although the use of this dose of intrathecal morphine has been shown to be associated with nausea in the absence of self-administered supplemental analgesics,¹⁴ a previous study involving parturients who had undergone cesarean delivery and received intrathecal morphine within the range of 0–0.5 mg found that nausea was not related to the dose of intrathecal morphine used.¹³

From the results of our study, it is unlikely that the higher incidence of nausea caused by neuraxial morphine had discouraged parturients of the AA genotype from self-administering morphine because there were correspondingly lower pain scores in patients of the AA genotype. Also, the total amount of PCA morphine used *per se* was unlikely to be a dominant factor in inducing nausea because the genotypic group that had used the highest amount of analgesics was associated with the lowest nausea scores. It is also debatable that as the result of disinclination to developing nausea, women with the GG genotype who had had greater pain scores to begin with were more willing to use PCA morphine to manage their pain. However, a previous study did not show an increased incidence of nausea despite a greater sensitivity of patients with the AA genotype to the analgesic effect of self-administered morphine in the postoperative period, although that study, which involved non-pregnant women after hysterectomy, was probably underpowered in this respect.⁷

We found that the incidence of pruritus was high, which was comparable to the figure reported in a previous systematic review.¹⁵ Also, a previous study showed that with the use of 0.2 mg intrathecal morphine, respiratory depression did not occur in more than 0.5% of parturients; most who were affected were markedly obese and had upper airway obstruction.¹⁶ Therefore, it is unsurprising that with the dose of intrathecal morphine that was used, our study, which did not include the markedly obese, did not detect any case of respiratory depression.

There is also evidence in the literature to suggest that individuals with the AA genotype are more susceptible to the central effects of morphine-6-glucuronide, an active metabolite of morphine that may accumulate in the body in the event of renal insufficiency.¹⁷ Indeed, at least

one report has demonstrated that the A118G polymorphism conferred variation in papillary constricting responses to morphine-6-glucuronide but not to morphine.¹⁸ Because we did not measure serum levels of morphine and its metabolite in this study, we were unable to determine whether our results could be attributed to an increase in analgesic response to this metabolite in AA individuals. However, as a result of the small dose of morphine used intrathecally, the contribution of neuraxial morphine to the plasma level of the metabolite is expected to be negligible. In addition, the use of PCA morphine was minimal, *i.e.*, mean of 9.4 mg or less over the 24-h period. Previous studies have shown that the contribution of morphine-6-glucuronide to analgesia in the context of short-term pain therapy with low doses of parenteral morphine is still debatable.¹⁹

Indeed, in our the multivariate analysis, we found that apart from genotype, age was a significant predictor of morphine consumption in the first 24 h after surgery even though our study did not include patients who were at the extremes of age. The correlation of increased patients' age with a reduction of morphine requirement for postoperative analgesia has been previously demonstrated.²⁰ Patients who were privately insured or self-paying, and hence were receiving private care from the health providers, also used less morphine. We were unable to exclude that this was due to a difference in the environment during hospitalization between paying and nonpaying patients. Although the incidence of having chronic pain has been associated with individuals who did not have private insurance in one study, the association of the paying status with the use of postoperative analgesia has not been reported.²¹ Our current model with OPRM genotypes accounts for less than 6% of the total variation in morphine consumption; this suggests that the contribution of other factors (including environmental and/or genetic factors plus their interaction) would need further investigation. Further studies to elucidate these factors and their influence on overall patient satisfaction are necessary to refine the individualization of acute postoperative analgesic therapy in this population.

Finally, although the clinical relevance of the small absolute difference in the mean consumption of PCA morphine in the first 24 h postoperatively among our study groups could be debated, it represents a near doubling of consumption in patients in the GG group in relation to their AA counterpart. Regardless of genotype, the usage of PCA morphine was greatest at the beginning and end of the first 24 h of the postoperative period, corresponding with the same trends in pain scores. This trend could be a reflection of the delayed peak effect of intrathecal morphine in the period in between as the residual analgesic effect rendered by the intrathecal local anesthetic wore off. The overall magnitude of pain experience, although statistically different among the ge-

notypes, was small. This was probably due to the efficacy of intrathecal morphine and rescue PCA morphine. Although the clinical significance of our findings could be debated, the potential of the A118G polymorphism to influence the perception of postoperative pain and its treatment, especially in the context of a significant difference in the incidence of side effects such as nausea, may not be dismissed.

In conclusion, our study showed that the A118G polymorphism of the human μ -opioid receptor has a significant effect on pain perception, analgesic requirement, and nausea for the first 24 h after cesarean delivery for patients who had received intrathecal and PCA intravenous morphine. Individuals with the AA genotype had less pain, required less PCA morphine, and experienced a higher incidence of nausea and vomiting. Further research and functional studies would be necessary to elucidate the clinical impact contributed by this genetic variation in the context of holistic treatment for acute postoperative pain management for this group of patients as well as the prevention of the development of chronic pain.²²

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