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ORIGINAL ARTICLE

Observational study of the effect of μ-opioid receptor genetic polymorphism on intrathecal opioid labor analgesia and post-cesarean delivery analgesia

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ABSTRACT
Background: The purpose of this two-part prospective observational and blinded trial was to determine whether the single nucleotide polymorphism of the μ-opioid receptor gene (OPRM1:c.304A>G) modifies (1) the duration of intrathecal fentanyl labor analgesia and (2) supplemental analgesic requirements after intrathecal morphine analgesia following cesarean delivery.
Methods: Labor analgesia was initiated with intrathecal fentanyl 25 μg. Patients undergoing primary cesarean delivery under spinal anesthesia received intrathecal morphine 150 μg. The primary outcome variables were duration of intrathecal fentanyl analgesia in the labor study and the requirement for supplemental systemic analgesia in the cesarean study. Outcomes were compared between 304A homozygotes (group A) and 304A>G heterozygotes and 304G homozygotes (group G).
Results: The labor study included 190 participants and the post-cesarean study included 103 participants; 24% subjects carried the 304A>G allele. The median (95% CI) duration of intrathecal fentanyl analgesia was 70 min (62, 78) in group A and 63 min (50, 76) in group G ($P = 0.54$). There was no difference in the amount of supplemental oral morphine equivalents required to treat breakthrough pain within 72 h after intrathecal morphine between groups A and G (median [IQR] 68 mg (37, 97) and 75 mg (37, 90) respectively, $P = 0.99$) or in the duration of intrathecal morphine analgesia ($P = 0.84$). The incidence of pruritus was greater in group A.
Conclusions: Using the two outcome parameters duration of analgesia and treatment for breakthrough pain, we did not find a simple association between intrathecal opioid analgesia and OPRM1 304A/G polymorphism.

Keywords: μ-opioid receptor polymorphism; Opioids; Opioid analgesia; Intrathecal analgesia; Obstetric analgesia; Labor analgesia; Cesarean delivery analgesia

Introduction

Pharmacogenetics is the study of the association between an individual's genetic profile and his/her response to drugs.[1] Several studies in animals and humans have suggested that the single nucleotide polymorphism (SNP) c.304A>G (initially known as c.118A>G, now annotated c.304A>G[2] and SNP rs1799971[3]) of the μ-opioid receptor gene (OPRM1) may influence individual response to opioid analgesia.[4] This mutation leads to a variant μ-opioid receptor in which an asparagine is substituted for aspartate as the 102[nd] amino acid of the receptor protein (p.Asn102Asp, previously known as p.N40D[5]).

The combined spinal-epidural (CSE) technique used for labor analgesia is commonly initiated with an intrathecal lipid-soluble opioid, usually fentanyl or sufentanil. The mean ± SD duration of analgesia after intrathecal fentanyl 25 μg is 89 ± 43 min.[6] The ED_{50} of intrathecal fentanyl for labor analgesia was 14 μg (95% CI 13 to 15 μg) in one study[6] and 18.2 μg (95% CI 17.5 to 18.8 μg) in a second.[7] The wide variability in duration of analgesia and reported ED_{50} may result from various individual differences known to affect labor pain, such as ethnicity, parity, stage of labor. Another possible explanation for differences in opioid requirements, as well as differences in incidence of side effects, pruritus, nausea and vomiting, is that opioid responsiveness is determined by genetic variability. Indeed, the ED_{50} of intrathecal fentanyl for labor analgesia was lower in parturients carrying the c.304A>G

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allele than in women homozygous for the wild-type allele.[8] However, to date, no studies have examined whether this potency difference results in differences in the clinical analgesic response to intrathecal fentanyl.

Intrathecal morphine is commonly used for post-cesarean analgesia. Several studies of postoperative analgesia have suggested that polymorphism at OPRM1:c. 304A>G influences requirements for i.v. morphine analgesia.[9–11] Until recently, the effect of this SNP on intrathecal morphine analgesia had not been reported.[12]

We designed two studies to test the hypotheses that the duration of intrathecal fentanyl labor analgesia and requirement for treatment of breakthrough pain after intrathecal morphine for post-cesarean analgesia differs in parturients with the SNP 304A>G compared to 304A of the OPRM1.

Methods

The studies were approved by the Institutional Review Boards of Northwestern University and the University Hospitals of Geneva.

DNA collection and SNP genotyping: At the time of study enrollment, before initiation of analgesia, venous blood was drawn into coded EDTA tubes. DNA purification and genotyping of OPRM1:c.304 were performed at the University Hospitals of Geneva and have been described previously.[8] Clinical care providers and subjects were blinded to genotype. Researchers performing the DNA analysis were blinded to subject clinical data.

Labor analgesia study: Term ($\geqslant$ 37 weeks of gestation) nulliparous women, ASA physical status 1 or 2, in spontaneous labor or with spontaneous rupture of membranes, and vertex presentation who planned neuraxial labor analgesia gave informed written consent to participate in the study shortly after admission to the labor and delivery unit of Prentice Women's Hospital in Chicago, IL. Exclusion criteria were chronic- or pregnancy-induced disease, chronic opioid use, history of substance abuse, systemic opioid analgesia before initiation of neuraxial labor analgesia, cervical dilation <2 cm or >5 cm at time of request for neuraxial analgesia, an allergy to fentanyl, or a contraindication to CSE analgesia. Women with failed intrathecal analgesia, defined as a visual analogue score (VAS) > 30 mm 10 min after the intrathecal injection (VAS for pain: 100 mm unmarked line where 0 mm = no pain and 100 mm = worst possible pain), were excluded from data analysis.

When the subject requested analgesia, cervical dilation was verified by digital examination performed by the obstetric provider or labor nurse. CSE analgesia was initiated with intrathecal fentanyl 25 μg (50 μg/mL, 0.5 mL), drawn up in a tuberculin syringe. No drugs were injected through the epidural catheter until the second request for analgesia. At this time the cervix was again examined, followed by initiation of epidural analgesia with a test dose (lidocaine 15 mg/mL with epinephrine 5 μg/mL, 3 mL) and bupivacaine (1.25 mg/mL, 10 – 15 mL). Analgesia was maintained with patient-controlled epidural analgesia (PCEA), bupivacaine 0.625 mg/mL with fentanyl 1.95 μg/mL: background infusion 15 mL/h, PCEA bolus 5 mL, lockout 10 min, maximum 30 mL/h) and breakthrough pain was treated with manual bolus injections of bupivacaine 1.25 mg/mL by the anesthesiologist. The study ended after delivery when the epidural infusion was discontinued.

The primary outcome variable was duration of intrathecal fentanyl analgesia, defined as the interval between the intrathecal injection and the second request for analgesia. VAS for pain were obtained by a research nurse immediately before initiation of neuraxial analgesia, 10 min after intrathecal injection, and at the second request for analgesia. In addition, at the second request for analgesia the parturient was asked about the presence of pruritus since the initiation of analgesia (none, mild, moderate, severe), nausea (none, mild, moderate or severe), and vomiting (yes, no). Approximately one hour after delivery the subject was asked to rate her satisfaction with labor analgesia (100 mm scale, 0 mm = not satisfied at all, 100 mm = very satisfied). In addition to maternal demographic data, the following data were collected: maximum oxytocin dose, time of complete cervical dilation (10 cm), time of delivery, mode of delivery, neonatal weight, Apgar scores and umbilical artery and vein blood gas values, total dose of epidural bupivacaine and other local anesthetics, total dose of epidural fentanyl, number of PCEA boluses and number of manual boluses (by the anesthesiologist).

Post-cesarean analgesia study: Healthy, term women admitted for planned primary cesarean delivery under spinal anesthesia gave informed written consent to participate in the study. Exclusion criteria were chronic- or pregnancy-induced disease, chronic opioid use, previous abdominal or pelvic surgery, allergy to fentanyl, morphine, or bupivacaine, body mass index $\geqslant$40 kg/m^2, or history of substance abuse.

Routine anesthesia care included (1) aspiration prophylaxis before initiation of anesthesia (i.v. ranitidine and metoclopramide, and oral antacid) and (2) spinal anesthesia with bupivacaine 12 mg (1.6 mL 0.75% hyperbaric bupivacaine), fentanyl 15 μg, and morphine 150 μg. Subjects with a sensory level to pinprick below T6, or those who required intraoperative systemic opioid supplementation, were excluded from further study participation. Subjects received ibuprofen 600 mg by mouth every 6 h starting in the post-anesthesia care unit and for 24 h after surgery. Patients were instructed to request rescue analgesia if they experienced discomfort. Rescue medication consisted of acetaminophen 325 mg/hydrocodone 10 mg tablets orally as needed every 4 h. An additional dose of acetaminophen/ hydrocodone was provided after 1 h if the pain was not relieved.