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ORIGINAL ARTICLE

Dose–response of intrathecal morphine when administered with intravenous ketorolac for post-cesarean analgesia: a two-center, prospective, randomized, blinded trial

J.S. Berger,[a,†] A. Gonzalez,[b,†] A. Hopkins,[a] T. Alshaeri,[c] D. Jeon,[a] S. Wang,[d] R.L. Amdur,[e] R. Smiley[f]

[a]*Department of Anesthesiology & Critical Care Medicine, The George Washington University School of Medicine and Health Sciences, Washington, DC, USA*
[b]*Department of Anesthesiology, Rutgers, New Jersey Medical School, Newark, NJ, USA*
[c]*Department of Anesthesiology, Wayne State University/Detroit Medical Center, Detroit, MI, USA*
[d]*Department of Biostatistics, Columbia University Mailman School of Public Health, New York, NY, USA*
[e]*Department of Surgery and Medical Faculty Associates, The George Washington University School of Medicine and Health Sciences, Washington, DC, USA*
[f]*Department of Anesthesiology, Columbia University College of Physicians and Surgeons, New York, NY, USA*

ABSTRACT

Background: The appropriate dose of intrathecal morphine for post-cesarean analgesia is unclear. With the inclusion of routine non-steroidal anti-inflammatory drugs, the required dose of morphine may be significantly less than the 200–300 μg common a decade ago. We performed a two-center, prospective, randomized, blinded trial comparing three doses of intrathecal morphine, combined with routine intravenous ketorolac, in 144 healthy women undergoing elective cesarean delivery.

Methods: Patients received an intrathecal injection of hyperbaric bupivacaine 12 mg, fentanyl 15 μg and a randomized dose of 50, 100, or 150 μg morphine in a volume of 2.2 mL. Patients received intravenous ketorolac 30 mg before leaving the operating room and 15 mg intravenously every 6 h for the duration of the study (24 h). All received postoperative patient-controlled intravenous morphine. The primary endpoint was total intravenous morphine administered postoperatively over 24 h, analyzed using mixed model regression.

Results: There were no differences between dose groups (or institutions) in intravenous morphine use over 24 h. Visual analog scale scores for pain and nausea did not differ. Pruritus was greater in the 100 and 150 μg groups than the 50 μg group at 6 h and 12 h, but there was no difference between groups in nausea or pruritus treatments. Respiratory depression or significant sedation did not occur.

Conclusion: The dose–response relationship of intrathecal morphine for multimodal post-cesarean analgesia suggests that 50 μg produces analgesia similar to that produced by either 100 μg or 150 μg.

Keywords: Cesarean delivery; Analgesia; Morphine; Intrathecal; Ketorolac

Introduction

There is significant variability between individuals in postoperative pain and analgesic use and in the efficacy of neuraxial opioid analgesics.[1,2] For women undergoing cesarean delivery, spinally-administered preservative-free morphine is suggested by the American Society of Anesthesiologists (ASA), and can provide up to 24 h of analgesia.[3] Post-cesarean pain management is unique because parturients must recover quickly in order to ambulate and care for their newborns.[4] Ideally, an optimal dose of morphine would maximize analgesic effects while minimizing side effects and permit safe ambulation. Common side effects of neuraxial morphine include

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Correspondence to: Jeffrey S. Berger, MD, MBA, 2300 Eye Street, NW, Suite 718, Washington, DC 20037, USA.
E-mail address: jberger@mfa.gwu.edu
† Joint first authors.

nausea, vomiting and pruritus. In rare cases, respiratory depression may occur.[5]

There have been few dose–response studies of intrathecal (IT) morphine, and most of these were performed before it became routine to administer adjuvant analgesics.[1] The now classic study by Palmer et al. examined IT morphine doses of 0, 25, 50, 75, 100, 200, 300, 400 and 500 μg and showed a threshold effect with morphine; that is, increasing doses of IT morphine over 100 μg did not enhance analgesia, but increased the incidence of side effects.[1] However, doses in the 200–300 μg range continue to be commonly used. Girgin et al. found no difference in the analgesic effectiveness of doses of IT morphine ranging from 100–400 μg, but there was decreased severity of side effects with lower doses.[6] A retrospective chart review by Wong et al. reported that IT morphine 200 μg provided better analgesia than 100 μg at the expense of increased nausea.[7] Similarly, a recent meta-analysis in which IT morphine doses were divided into two groups, low dose (50–100 μg) and high dose (>100–250 μg), showed prolonged analgesia at the expense of greater side effects in those patients receiving high dose.[8]

Thus, the minimal effective dose of morphine using multimodal analgesia in an obstetric setting remains unclear. We have performed a two-center, prospective, blinded, randomized clinical trial to determine the dose–response relationship of IT morphine, when co-administered with intravenous ketorolac for post-cesarean analgesia, evaluating both analgesic efficiency and occurrence of side effects.

Methods

The Institutional Review Boards of The George Washington University and Columbia University approved the study. The trial was registered with the ClinicalTrials.gov registry by the Principal Investigator (RMS) on November 2, 2011 (NCT01465191). To clarify the pre-trial intention to conduct an interim analysis, the registry was updated on January 15, 2015.

This is an interim analysis of an ongoing study with two main outcome goals: to determine the dose–response of IT morphine when combined with routine intravenous ketorolac after cesarean delivery, and to examine the effect of mu-opioid receptor genotype variation on the dose–response.[9] The complete study including the genetic analysis requires 300 patients, but the simple dose–response study was determined to require about 150 patients.

After written informed consent, 144 women undergoing elective cesarean delivery were enrolled in this prospective, randomized, blinded trial. Inclusion criteria were ASA physical status <3, age 18–45 years, term pregnancy (≥37 weeks of gestation), height ≥147 cm and body mass index (BMI) <45 kg/m^2. Exclusion criteria were patient refusal, significant medical disease (ASA physical status 3 or more), urgent/emergent cesarean delivery, allergy or contraindication to ketorolac or morphine, and any patient receiving analgesics or with an acute or chronic pain syndrome. Each participant was randomized based on a computer-generated table of random numbers, with her dose assignment placed in an opaque envelope that was opened immediately before preparation of the spinal anesthetic dose. Patients were assigned to one of three treatment groups to receive 50, 100, or 150 μg (0.1, 0.2 and 0.3 mL, respectively) of IT morphine with hyperbaric bupivacaine 12 mg and fentanyl 15 μg (0.3 mL) in a total volume of 2.2 mL with saline if necessary. The morphine, fentanyl and saline doses were drawn into a 1 mL syringe for accuracy, and added to the spinal injection syringe containing 0.75% hyperbaric bupivacaine 1.6 mL. The patient, clinical care team, and the investigators performing all study-related assessments were blinded to the treatment group.

All patients received an oral non-particulate antacid and 500–1000 mL lactated Ringer's solution before anesthesia administration. Spinal or combined spinal-epidural (CSE) anesthesia was administered with the patient in the sitting position, at an interspace judged to be L3–4 or L4–5 using a 25-gauge Whitacre spinal needle. Upon return of clear cerebrospinal fluid, bupivacaine, fentanyl, and the morphine dose according to the patient's group assignment was injected. After injection, the spinal needle was withdrawn, an epidural catheter was inserted if a CSE technique was used, and the patient was placed in the supine position with left tilt. Maternal blood pressure was monitored every 1–2 min, until delivery of the baby, after which blood pressure was monitored every 5 min at the provider's discretion. Surgery started following temperature or pin-prick testing to a T4 level in conjunction with a negative Allis clamp test of sensory blockade in four abdominal quadrants. After delivery of the baby, oxytocin was slowly infused using a standard concentration of 20 U in 500 mL. If the patient received CSE anesthesia, the epidural catheter was removed at the end of the surgery, before exiting the operating room. Patients received intravenous ketorolac 30 mg before leaving the operating room and 15 mg intravenously every 6 h for the 24-h duration of the study. The anesthesiologist who prepared the dose of morphine was not involved further in the care or assessment of the patient.

After surgery, the patient was provided with an intravenous patient-controlled analgesia (PCA) pump programmed to supply a 1.0 mg morphine bolus with a 6-min lockout time, 10 mg/h maximum dose, and no continuous infusion. The interval from administration of IT morphine to first demand for PCA morphine was recorded, and cumulative usage was recorded every 6 h. Visual analog scale (VAS) scores for pain were

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