International Journal of Obstetric Anesthesia (2011) **20**, 3–9
0959-289X/$ - see front matter
doi:10.1016/j.ijoa.2010.10.002

ELSEVIER
www.obstetanesthesia.com

ORIGINAL ARTICLE

Low-dose ketamine with multimodal postcesarean delivery analgesia: a randomized controlled trial

J.R. Bauchat, N. Higgins, K.G. Wojciechowski, R.J. McCarthy, P. Toledo, C.A. Wong
Department of Anesthesiology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

ABSTRACT
Background: Ketamine at subanesthetic doses has analgesic properties that have been shown to reduce postoperative pain and morphine consumption. We hypothesized that intravenous ketamine 10 mg administered during spinal anesthesia for cesarean delivery, in addition to intrathecal morphine and intravenous ketorolac, would decrease the incidence of breakthrough pain and need for supplemental postoperative analgesia.
Methods: Using a randomized double-blind placebo-controlled design, healthy women scheduled for cesarean delivery receiving hyperbaric spinal bupivacaine, fentanyl and morphine were randomized to intravenous ketamine 10 mg or saline following delivery. Postoperative analgesia included scheduled ketorolac and acetaminophen/hydrocodone tablets as needed for breakthrough pain. The primary outcome was the incidence of breakthrough pain in the first 24 h. Secondary outcomes included the number of acetaminophen/hydrocodone tablets administered and numeric rating scale for pain (0–10).
Results: Group characteristics did not differ. There was no difference in the incidence of breakthrough pain (ketamine 75% VS. saline 74%, $P = 0.86$). There was no difference in 24-h or 72-h use of supplemental acetaminophen/hydrocodone tablets between groups. Pain scores in the first 24 h were similar, but lower in the ketamine compared to the saline group 2 weeks postpartum (difference −0.6, 95% CI −1.1 to −0.9).
Conclusions: We found no additional postoperative analgesic benefit of low-dose ketamine during cesarean delivery in patients who received intrathecal morphine and intravenous ketorolac. Subjects who received ketamine reported lower pain scores 2 weeks postpartum.

Keywords: Ketamine; Cesarean section; Cesarean delivery; Postoperative analgesia

Introduction

Effective analgesia following cesarean delivery is important to provide maternal comfort as well as to increase mobility, reduce the risk of deep vein thrombosis, and aid in the mother's ability to care for her infant.[1] Multimodal postoperative analgesia is utilized to block multiple nociceptive pathways while minimizing the side effects experienced with fewer drugs used at higher doses. Opioids transfer into breast milk and although the clinical relevance to the infant is debated, it seems prudent to minimize maternal intake of these medications.[2,3]

Accepted October 2010
Presented at the Society for Obstetric Anesthesia and Perinatology 41st Annual Meeting, Washington, DC, 2009.
Correspondence to: Jeanette R. Bauchat, M.D. Department of Anesthesiology, Northwestern University Feinberg School of Medicine, 251 E. Huron St., Feinberg 5-704, Chicago 60611, IL, USA.
E-mail address: j-bauchat@northwestern.edu

Ketamine, an *N*-methyl-D-aspartate (NMDA) antagonist, when used in subanesthetic doses, has analgesic properties that have been used for treatment of acute and chronic pain. Multiple clinical trials of ketamine administered during surgery performed under general anesthesia demonstrate opioid-sparing effects and reduced pain scores in the acute postoperative setting. A 2006 Cochrane review concluded: "Ketamine in subanesthetic doses is effective in reducing morphine requirements in the first 24 h after surgery."[4] In addition to intrinsic analgesia activity, ketamine may also decrease 24-h morphine consumption by preventing acute opioid tolerance.[5]

Reduced postoperative opioid requirements have been observed when intravenous (i.v.) ketamine, versus thiopental, was used as an induction agent for cesarean delivery.[6] This effect was also seen when subanesthetic doses of i.v. ketamine (0.15 mg/kg) were administered during general or spinal anesthesia for cesarean delivery.[7,8] To our knowledge, the opioid-sparing effects of subanesthetic doses of ketamine in the setting of

cesarean delivery under spinal anesthesia in patients receiving a multimodal analgesic regimen, including intrathecal morphine, has not been studied.

We hypothesized that administering a single low dose of i.v. ketamine during spinal anesthesia for cesarean delivery, in addition to our standard postoperative analgesic regimen (intrathecal morphine with scheduled i.v. ketorolac), would decrease the incidence of breakthrough pain in the first 24 h postoperatively. The aim of this randomized placebo-controlled trial was to evaluate the incidence of breakthrough pain as well as the need for supplemental analgesia in patients receiving ketamine versus placebo.

Methods

This protocol was approved by the Northwestern University Institutional Review Board and registered with Clinicaltrials.gov (NCT00486902). The trial was conducted at Prentice Women's Hospital. Women $\geqslant$ 37 weeks of gestation, ASA physical status 1–2, scheduled for elective cesarean delivery whose anesthetic plan included spinal anesthesia with intrathecal morphine and i.v. ketorolac for postoperative analgesia were approached for study participation. Women were excluded if their body mass index was $\geqslant$40 kg/m^2 or if they had allergies to any of the study medications, contraindications to spinal anesthesia, or history of hallucinations, substance abuse, chronic opioid therapy or chronic pain. Data were not analyzed from patients whose anesthetic was converted to general anesthesia, or who required intravenous supplementation during cesarean delivery, or postoperative intensive care.

Randomization assignments were from a computer-generated random number table. Group allocations were placed in sequentially numbered opaque envelopes. A research nurse or anesthesiologist not involved in the patient's care opened the envelope after informed written consent was obtained and prepared the study solution. Subjects randomized to the treatment group received i.v. ketamine 10 mg diluted to 20 mL with 0.9% saline. Subjects randomized to the placebo group received 20 mL of 0.9% saline.

An anesthesiologist blinded to group allocation initiated spinal anesthesia at the L3–4 interspace ($\pm$ one vertebral interspace) with the patient in the sitting position. All patients received intrathecal hyperbaric bupivacaine 12 mg (1.6 mL 0.75% bupivacaine in 5% dextrose), fentanyl 15 μg and morphine 150 μg as a single injection. The subject was placed supine with left lateral tilt and cesarean delivery commenced after confirmation of a T4 sensory level to pinprick. Vasopressors and i.v. fluids were administered at the anesthesiologist's discretion.

Five minutes after delivery of the infant, the study drug was administered over 10 min via an infusion pump set at 2 mL/min. Five minutes after complete administration of the study drug the anesthesiologist asked the subject if she had nausea, vomiting or pruritus. Nausea and pruritus were graded as none, mild, moderate or severe; and vomiting as present or absent. In addition, sedation was assessed using the Richmond agitation-sedation scale and spontaneous complaints of psychomimetic effects were noted at this time.[9]

Upon completion of the cesarean delivery, subjects were transported to the post-anesthesia care unit (PACU) with standard postoperative orders. Patients received i.v. ketorolac 30 mg every 6 h for 24 h, the first dose given in the PACU, but were allowed to refuse these scheduled analgesic interventions. Patients were instructed to request rescue analgesia if they experienced discomfort. Rescue medication consisted of 1 tablet of acetaminophen 325 mg/hydrocodone 10 mg every 4 h as needed. An additional tablet of acetaminophen/hydrocodone was provided after 1 h if the pain was not relieved to the subject's satisfaction. Breakthrough pain was defined as a request by the patient for supplemental pain medication in the first 24 h. Pain was assessed by study personnel using numeric rating scale (NRS) pain scores at regular intervals in the first 24 h after administration of the study drug. The presence and severity of nausea, vomiting, and pruritus was assessed at the same time intervals. Between 24 and 72 h, analgesia was provided at the patients' request with ibuprofen 600 mg every 6 h and 1–2 tablets of acetaminophen 325 mg/hydrocodone 10 mg every 4 h.

The subjective psychomimetic effects of ketamine were assessed at 1 and 4 h using a set of true/false questions from the lysergic acid diethylamine (LSD) short form of the Addiction Research Center Inventory (ARCI).[10] This validated tool was designed to assess subjective experiences of patients receiving different classes of drugs, including opioids and LSD. Drugs from different classes can be distinguished from one another by a higher percentage of "true" answers in one category of drug compared to another. The effects of ketamine have been validated using the LSD-ARCI questions.

Subject characteristics, including maternal age, height, weight, pre-pregnancy weight, gestational age and i.v. fluid volume administered during cesarean delivery were recorded. At 24 and 72 h subjects were asked about satisfaction with postoperative analgesia (0–10 scale where 0 = not at all satisfied, 10 = very satisfied). At 72 h, they were asked about disturbing dreams during the postoperative period. The study ended 2 weeks postpartum with a telephone follow-up evaluation that assessed satisfaction with analgesia overall and average pain score at that time.

Statistical analysis

Sample size was determined assuming a baseline incidence of breakthrough pain of 75% and an absolute difference between groups of -20% to $+15\%$. This rate of request for analgesia in the first 24 h was based on data