Analgesic Efficacy of Two Doses of Intrathecal Midazolam With Bupivacaine in Patients Undergoing Cesarean Delivery

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Objectives: In this prospective, randomized, double-blind, placebo-controlled study, we investigated the postoperative analgesic efficacy of 2 doses of intrathecal midazolam as an adjunct to bupivacaine for spinal anesthesia.

Methods: Sixty patients undergoing elective cesarean delivery under spinal anesthesia were allocated randomly to 3 groups: group B, 2 mL hyperbaric bupivicaine 0.5%; group BM1, 2 mL bupivacaine plus midazolam 1 mg (preservative free); and group BM2, 2 mL bupivicaine plus midazolam 2 mg.

Results: The mean duration of postoperative analgesia (determined by request for rescue medication) was 3.8 ± 0.5 hours in group B compared with 4.3 ± 0.7 hours in group BM1 ($P = .18$), and 6.1 ± 1.0 hours in group BM2 ($P = .001$). Supplemental analgesic requirements with diclofenac were significantly less in group BM2 (93 ± 29 mg) compared with group B (145 ± 12 mg) and group BM1 (148 ± 16 mg, $P < .001$). Time to block regression was longer in group B (182 ± 30 minutes) compared with group BM1 (152 ± 32 minutes) and group B (126 ± 20 minutes) (both $P < .001$). Arterial pressure, heart rate, oxygen saturation, sedation score, and time to first void were comparable between groups. Group B had a significantly higher incidence of nausea and vomiting than groups BM1 and BM2 ($P = .02$). No neurologic deficits were observed.

Conclusions: Intrathecal midazolam 2 mg provided a moderate prolongation of postoperative analgesia when used as an adjunct to bupivacaine in patients undergoing cesarean delivery. Intrathecal midazolam, 1 mg and 2 mg, decreased postoperative nausea and vomiting. *Reg Anesth Pain Med 2006;31:221-226.*

Key Words: Analgesia, Obstetric, Postoperative, Anesthetic techniques, Intrathecal, Anesthetics, Local, Bupivacaine, Analgesics, Midazolam.

Spinal anesthesia with bupivacaine is a common analgesic technique used in obstetric anesthesia practice. Its advantages for lower-segment cesarean delivery (CD) are its simplicity, speed, reliability, minimal exposure to depressant drugs, and its ability to minimize the hazards of difficult intubation and aspiration. However, a single intrathecal injection of bupivacaine provides analgesia for only 2.5 to 3 hours.[1] Most patients require further analgesia during the postoperative period.

Various adjuvants to intrathecal local anesthetics such as epinephrine, opioids, alpha-2 adrenergic agonists, neostigmine, and midazolam have been used to prolong the duration of postoperative analgesia. Midazolam is a potent short-acting imidazobenzodiazepine that has been shown to have antinociceptive effects when administered intrathecally, both in laboratory animals[2,3] and in humans.[4-7] Doses up to 2 mg have been described without adverse effects.[5] There are no available data comparing the efficacy of intrathecal midazolam 1 mg and 2 mg in the obstetric population. This study tested the hypothesis that intrathecal midazolam would improve analgesia when coadministered with bupivacaine while reducing postoperative analgesic requirements. The purpose of this prospective, randomized, double-blind, placebo-controlled study was to evaluate the postoperative analgesic efficacy of 2 doses of intrathecal midazolam as an adjunct to bupivacaine 0.5% in patients undergoing elective CD.

Methods

After approval by our hospital ethics committee and obtaining written informed consent, we studied

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60 patients, American Society of Anesthesiologists classification physical status 1 and 2, scheduled for elective cesarean delivery under spinal anesthesia. Patients were excluded from the study if there was a contraindication to regional anesthesia, known sensitivity to study drugs, or they were receiving chronic analgesic therapy. Fetal prematurity (less than 36 weeks' gestation) was also considered a contraindication.

All patients were fasted and received oral ranitidine 150 mg the night before and the morning of surgery. Metoclopramide 10 mg was administered intravenously 30 minutes before anesthesia. A visual analog scale (VAS) consisting of a 100-mm line, in which 0 represented no pain and 100 represented the worst possible pain, was explained to all patients in their preoperative visit.

Patients were randomly allocated to 1 of 3 groups: group B received 2 mL hyperbaric bupivacaine 0.5% in 8% dextrose and 0.4 mL saline, group BM1 received 2 mL bupivacaine 0.5% combined with 0.2 mL midazolam (5 mg/mL) and 0.2 mL saline, and group BM2 received 2 mL bupivacaine 0.5% combined with 0.4 mL midazolam (5 mg/mL). Preservative-free midazolam (Mezolam; Neon Laboratories, Mumbai, India) was used. Active and placebo solutions were prepared by a staff anesthetist not involved in the study.

Standard monitoring was established with electrocardiography, pulse oximetry, and noninvasive arterial pressure measures. An 18-G intravenous cannula was sited and a preload of 500 mL Ringer's lactate solution was administered. Spinal anesthesia was performed in the sitting position with a 25-G Quincke spinal needle (Spinocan; B Braun, Melsungen, Germany) using the midline approach at the L3-4 level. After free flow of cerebrospinal fluid was obtained, the study solution was administered. The level of sensory anesthesia, defined as the loss of sharp sensation with the use of a pinprick test with a short-beveled needle, was recorded at 2-minute intervals for 15 minutes after completion of intrathecal injection and thereafter every 10 minutes. A dermatomal sensory block up to T4 was considered adequate for surgery.

Intraoperatively, heart rate, arterial pressure, and respiratory rate were monitored every 5 minutes, and oxygen saturation and electrocardiography were monitored continuously. Bolus doses of ephedrine 6 mg were given intravenously as required to maintain arterial pressure within 15% of baseline systolic arterial pressure. Lower-segment CD was performed through a Pfannenstiel incision. Oxytocin (5 U bolus and 10 U in 500 mL 5% dextrose solution at 30 drops/min) was administered at the time of umbilical cord clamping. Apgar score was recorded at 1 and 5 minutes after delivery. VAS scores assessment for postoperative pain were made by the anesthesiologist at 1, 2, 3, 4, 5, 6, and 24 hours. Between 6 hours and 24 hours, VAS score was evaluated by the nursing staff. Diclofenac 1 mg/kg intramuscularly was administered as rescue analgesic on patient demand or when VAS score exceeded 40 mm.

Time to first analgesic (time between intrathecal injection and first administration of rescue analgesia) and the total number of analgesic doses required in the first 24 hours were recorded. Assessment of sedation (wide awake = 0, sleeping comfortably but responding to verbal commands = 1, deep sleep but arousable = 2, deep sleep but not arousable = 3)[8] was performed at 1, 6, and 24 hours after arrival in the recovery room. Time to regression of anesthesia was determined as the point at which the cephalad level of sensory anesthesia receded 2 segments.[9] Time to first void, neurologic deficits, and adverse effects (nausea, emesis, and pruritus) were recorded. Symptoms suggestive of neurologic damage such as back pain, pain, numbness or weakness in legs, and bladder or bowel dysfunction were recorded postoperatively at 24 hours.

To assess the difference among the groups for continuous variables, 1-way analysis of variance was used with post hoc (Bonferroni) analysis. For finding association among the categorical variables, a chi-square test was applied. To assess the trend within the variables, 2-way analysis of variance was used. $P < .05$ was regarded as statistically significant. Statistical software SAS 8.0 (SAS Institute Inc, Cary, NC) was used for statistical analysis. Power analysis was not performed; rather, sample size was based on estimated enrollment over a 6-month period. A post hoc power analysis showed that the study had 78% power to show any difference in the duration of analgesia between the groups at $P < .05$.

Results

There were no significant differences between the groups in patient characteristics or duration of surgery (Table 1). No clinically significant changes were observed in heart rate, arterial pressure, respiratory rate, oxygen saturation, and sedation score in the 3 groups, both intraoperatively and postoperatively.

Mean time to first administration of rescue analgesia was 3.8 ± 0.5 hours in group B, 4.3 ± 0.7 hours in group BM1, and 6.1 ± 1.0 hours in group BM2 ($P = .001$). Time to first rescue analgesia in group BM2 was significantly greater than that in group BM1 and group B ($P = .001$). Time to first

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