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Effects of Intrathecal Midazolam on Postoperative Analgesia When Added to a Bupivacaine-Clonidine Mixture

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Background: Previous clinical and experimental studies have shown that a midazolam-clonidine mixture has a synergistic antinociceptive effect. This study evaluated the postoperative analgesic effect of adding midazolam to an intrathecal bupivacaine-clonidine mixture.

Methods: One hundred ten patients scheduled to undergo elective lower-extremity surgery were enrolled in this double-blind, randomized trial. Spinal anesthesia was administered by using 1 of 2 mixtures. Group B-C received 12.5 mg isobaric 0.5% bupivacaine, 30 μg clonidine, and 0.4 mL 0.9% saline. Group B-C-M received the B-C mixture plus 2 mg of midazolam in a 0.4-mL solution. Motor and sensory block levels were assessed before, during, and after the procedure until regression of the block to S2. Sedation levels were determined before anesthesia, during surgery, and at the end of the procedure. Postoperative analgesia was assessed every 15 minutes by using a visual analog scale. Duration of sensory and motor blocks was determined based on a modified Bromage scale, and time of the first pain relief request was noted.

Results: Duration of sensory block, time of first postoperative analgesic request, and amount of postoperative morphine administered were comparable between groups. However, the motor blockade lasted significantly longer in the B-C-M group compared with the B-C group (287 $\pm$ 73 minutes vs 257 $\pm$ 72 minutes, respectively; $P < .05$).

Conclusion: Addition of midazolam to an intrathecal B-C mixture does not potentiate postoperative analgesia but prolongs the motor blockade. *Reg Anesth Pain Med 2006;31:501-505.*

Key Words: Midazolam, Intrathecal anesthesia, Postoperative analgesia.

Several adjuvant drugs have been injected with intrathecal anesthesia to prolong postoperative analgesia, but many of these drug combinations produce significant side effects. Opioids prolong the duration of spinal anesthesia without delaying recovery to ambulation, and clonidine provides a coanalgesic effect, decreasing postoperative analgesic requirement and improving analgesic quality.[1-3] However, many significant side effects limit their use, including respiratory depression, hemodynamic instability, pruritus, urinary retention, nausea and vomiting, and sedation.[4,5]

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Several clinical studies have shown that midazolam can be safely added to intrathecal local anesthetics to improve postoperative analgesia with minimal side effects.[6-11] For this study, we postulated that adding midazolam to an intrathecal bupivacaine-clonidine mixture would prolong postoperative analgesia. To test this hypothesis, we administered spinal anesthesia to 2 groups of patients undergoing lower extremity surgery: group B-C received a bupivacaine-clonidine mixture only,

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and group B-C-M received the B-C mixture plus midazolam.

Materials and Methods

After obtaining approval of the Medical Ethics Committee at Aziza Othmana Hospital where the study was conducted and written informed consent from each subject, 110 American Society of Anesthesiologists I to III patients scheduled to undergo elective lower-extremity surgery were enrolled in this double-blind, randomized trial. Criteria for study exclusion were any contraindication to regional anesthesia, chronic analgesic therapy with opioids or constant baseline pain score >40/100, serious spinal abnormality, or peripheral neuropathy.

The anesthesia protocol was standardized; no premedication was given. Patients received 500 mL 0.9% saline as fluid loaded over 20 minutes, and a Whitacre 25-gauge atraumatic needle was inserted at the L3-L4 intervertebral space with the patient in the sitting position. We administered anesthesia by using 1 of 2 intrathecal mixtures. Group B-C received 12.5 mg isobaric 0.5% bupivacaine with 30 μg clonidine plus 0.4 mL 0.9% saline, and group B-C-M received 12.5 mg isobaric 0.5% bupivacaine with 30 μg clonidine and 2 mg buffered preservative-free midazolam in a 0.4-mL solution (Hypnovel; Roche, Neuilly-sur-Seine, France). The total volume of each intrathecal injection was 3.9 mL. These solutions were prepared and blinded by a pharmacist independent of the study. The density of the intrathecal solutions (B-C and B-C-M) was measured at room temperature by using a picnometric technique.

We monitored vital signs until each patient was discharged from the recovery room. An electrocardiogram and arterial oxygen saturation were recorded continuously by using a Datex Cardiocap monitor (Ohmeda, Madison, WI). Blood pressure was measured noninvasively every 5 minutes until the end of the surgical procedure and every 20 minutes thereafter. Intravenous crystalloids and ephedrine (in 3-mg increments) were given to treat hypotension (systolic blood pressure <70 mm Hg or >30% decrease from preanesthesia values).

Motor and sensory block levels were assessed at 5, 10, 20, 40, and 60 minutes after intrathecal injection; at the end of the surgical procedure; and every 15 minutes thereafter until regression to S2. All assessments were performed by physicians blinded to the subjects' study group. Motor block levels were based on a 6-point modified Bromage scale as follows: 1, complete motor block; 2, almost complete blockade (the patient is able to move his/her feet only); 3, partial motor blockade (the patient is able to move his/her knees); 4, detectable weakness of hip flexion (the patient is able to raise his/her leg but is unable to keep it raised); 5, no detectable weakness of hip flexion; and 6, no weakness at all. Motor block was considered effective when the Bromage score was ≤2. Sensory block was assessed by pinprick testing.

Sedation levels were evaluated before anesthesia, every 15 minutes during surgery, and at the end of the procedure by using a 4-point scale as follows: 1, awake; 2, drowsy but responsive to verbal command; 3, drowsy but responsive to physical stimulus; and 4, unresponsive to verbal and physical stimuli.

Postoperative analgesia was assessed every 15 minutes by using a visual analog scale (VAS) from 0 to 100 mm (0 = no pain at all and 100 = maximum imaginable pain). When the VAS score was ≥40 mm, analgesia was provided with 1 mg intravenous morphine every 3 minutes until adequate pain relief was achieved.

Patients stayed in the recovery room until the sensory block regressed below L1 (assessed by pinprick) and voluntary movements in the lower extremities returned. Onset of sensory and motor blocks, duration of sensory and motor blocks, length of surgical procedure, and time of first pain relief request were recorded.

To diagnose possible neurologic complications,

Table 1. Demographic and Perioperative Data

Parameter	Bupivacaine Clonidine (n = 55)	Bupivacaine Clonidine Midazolam (n = 55)
Age (y)	51 ± 19	49 ± 20
Sex (M/F), n	30/25	28/27
Weight (kg)	74 ± 14	71 ± 10
Height (cm)	170 ± 8	169 ± 8
Surgery, n		
Femur	20	19
Knee	21	16
Tibia and ankle	14	20
Surgery duration (min)	76 ± 35	79 ± 37
Density of intrathecal solution (kg/m^3)	1,005	1,005
Mean arterial pressure (mm Hg)		
Before surgery	101 ± 18	98 ± 14
During surgery	83 ± 10	82 ± 10
End of surgery*	83 ± 9	79 ± 15
Heart rate (beats/min)		
Before surgery	89 ± 12	88 ± 16
During surgery	83 ± 14	82 ± 15
End of surgery	82 ± 14	78 ± 14
Volume loading (mL)	1,465 ± 506	1,555 ± 696
Ephedrine (mg)	7 ± 12	4 ± 10

NOTE. Values are means ± standard deviation unless otherwise indicated.

*P = .047.