Original Article

Addition of low-dose ketamine to midazolam and low-dose bupivacaine improves hemodynamics and postoperative analgesia during spinal anesthesia for cesarean section

Ahmed Sobhy Basuni

Department of Anesthesiology and Intensive Care, Faculty of Medicine, Tanta University, Tanta, Egypt

Abstract

Background and Aims: Spinal anesthesia for cesarean section (CS) is associated with an incidence of hypotension of 60-94%. This study hypothesizes that intrathecal combination of low-dose ketamine, midazolam, and low-dose bupivacaine improves hemodynamics and postoperative analgesia compared with fentanyl and low-dose bupivacaine during CS.

Material and Methods: Fifty parturients undergoing elective CS were randomized equally to receive ketamine (10 mg), midazolam (2 mg) and 0.5% hyperbaric bupivacaine (8 mg) in group ketamine-midazolam-bupivacaine (KMB) or fentanyl (25 μg) and 0.5% hyperbaric bupivacaine (8 mg) in group fentanyl-bupivacaine (FB). Heart rate (HR), mean arterial blood pressure (MAP), oxygen saturation, sensorimotor block characteristics, pain-free period, side-effects including: hypotension, bradycardia, nausea, vomiting, sedation, pruritus, respiratory depression and dissociative manifestations, Apgar score at 1 and 5 min, and patients' satisfaction visual analog scores (VAS) were recorded. Patients in group KMB were followed for 6 months in order to assess any neurological disorder.

Results: Group KMB showed higher sensory level ($P = 0.006$), rapid sensory ($P = 0.001$) and motor ($P = 0.005$) onsets, prolonged sensory ($P = 0.008$) and motor ($P = 0.002$) blocks, and prolonged pain free period ($P = 0.002$). Ketamine-midazolam stabilized HR and MAP, and significantly reduced incidence of hypotension ($P = 0.002$), bradycardia ($P = 0.013$) and vomiting ($P = 0.019$). Apgar scores at 1 and 5 min were comparable in both groups ($P = 0.699$ and 0.646 respectively). Patients' satisfaction VAS scores were significantly higher in group KMB ($P = 0.001$). No patients in KMB group showed dissociative or neurotoxic manifestations.

Conclusion: Intrathecal low-dose ketamine combined with midazolam and low-dose bupivacaine stabilizes hemodynamics and prolongs postoperative analgesia without significant side-effects in parturients undergoing CS.

Key words: Cesarean section, intrathecal ketamine, intrathecal low-dose bupivacaine, intrathecal midazolam

Introduction

Spinal anesthesia is the preferred technique for cesarean section (CS) owing to its benefits of simplicity, reliability, low rates of airway complications and aspiration, facilitation of postoperative analgesia, less neonatal exposure to potentially depressant drugs, and awake mother at the time of the birth of the child that establishes maternal-infant bonding and successful breastfeeding. However, spinal anesthesia has been associated with an incidence of maternal hypotension of 60-94%.[1] Hypotension impairs uteroplacental circulation and frequently results in nausea, vomiting and organ-system disorders particularly in the presence of coexisting diseases.

Arzola and Wieczorek, in a systematic review and meta-analysis, demonstrated that low-dose bupivacaine (≤8 mg) in combination with fentanyl (≤25 μg) significantly reduces incidence of hypotension and bradycardia during spinal anesthesia for CS, but compromises surgical analgesia and increases the need for intra-operative supplemental analgesia.[2]

Intrathecal midazolam enhances the anesthetic effect of bupivacaine without affecting the hemodynamics.[3,4] Although ketamine stabilizes hemodynamics it has a limited analgesic effect and is associated with a higher incidence of dissociative

Address for correspondence: Dr. Ahmed Sobhy Basuni, Department of Anesthesiology and Intensive Care, Faculty of Medicine, Tanta University, Tanta, Egypt.
E-mail: Ahmed.basuni@med.tanta.edu.eg

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manifestations.[5,6] Midazolam combined with low-dose ketamine as a neuraxial adjuvant to bupivacaine has been shown to reduce hemodynamic fluctuations and prolong postoperative analgesia in orthopedic surgery without significant adverse effects.[7] This study was performed to evaluate the effect of low-dose ketamine combined with midazolam compared with fentanyl as adjuvants to intrathecal low-dose bupivacaine for CS on hemodynamics and postoperative analgesia.

Material and Methods

After obtaining Institutional Review Board approval and written informed consent, this prospective double-blinded study was conducted from May 2012 to February 2013. Fifty parturients aged between 20 and 40 years undergoing elective lower segment transverse incision CS of singleton pregnancy at >36 gestational weeks by a single surgeon were consecutively enrolled. Patients were excluded from the study if they had height <150 cm or >180 cm, a hypertensive disorder of pregnancy (chronic hypertension, gestational hypertension, preeclampsia, or preeclampsia superimposed on chronic hypertension), antepartum hemorrhage, evidence of acute fetal distress, thyrotoxicosis, valvular heart disease, asthma, chronic obstructive pulmonary disease, other organ-system disease, neuromuscular or psychological disorders, allergy to the study medications, or contraindication to spinal anesthesia. Randomization was done using a computer generated random number table into two equal groups (ketamine-midazolam-bupivacaine [KMB] and FB). Allocation to groups was concealed using sequentially numbered, opaque, sealed envelopes.

Oral ranitidine 50 mg was administered with a sip of water 2 h before surgery. An anesthetist not involved with intra-operative care or measurements prepared the study medications according to the randomization protocol. Patients in group KMB received 10 mg (0.2 mL) ketamine (Ketam, EIPICO, Egypt, 50 mg/mL), 2 mg (0.4 mL) midazolam (Dormicum, Roche, Switzerland, 5 mg/mL) and 8 mg (1.6 mL) hyperbaric bupivacaine (Marcaine, Astra Zeneca, France, 0.5%); those in group FB received 25 μg (0.5 mL) fentanyl (Fentanyl, Hameln pharmaceutical, Germany, 50 ug/mL) and 8 mg (1.6 mL) hyperbaric bupivacaine 0.5%. The medications were diluted in saline to a total volume of 3 mL and stored in identical syringes that were placed on a sterile spinal anesthesia tray and covered with a sterile drape to prevent contamination.

Monitoring included heart rate (HR), noninvasive blood pressure, oxygen saturation (SpO_2) and electrocardiography. Patients were preloaded with Ringer's lactate 500 ml and lumbar puncture was performed in the sitting position at L4-L5 or L3-L4 intervertebral space with a 25-G spinal needle under the strict aseptic precaution. The medications were injected over 10 s with no barbotage and the needle orifice cephalad. After intrathecal injection, patients were immediately placed supine with left uterine displacement and received 100% O_2 (4 L/min) with face mask. After the delivery of the fetus, they oxytocin 20 IU was added to the intravenous (IV) fluids. The surgeon exteriorized the uterus in all patients. Intra-operative pain or discomfort after delivery was managed with 1 ug/kg fentanyl IV. If the patient complained of pain before delivery or fentanyl failed to relieve pain after delivery, general anesthesia was administered, and the patient was excluded from the study.

Heart rate, mean arterial blood pressure (MAP), and SpO_2 were recorded before lumbar puncture, every 5 min during the first 30 min, then 45 min, 60 min, 2 h and 4 h after intrathecal injection. Sensory block was tested every 2 min with pinprick test in the mid-clavicular line, bilaterally, until it stabilized for three consecutive tests; then every 15 min till block regression to S1. Motor block was tested by the modified Bromage scale (0: No motor loss, 1: Inability to flex hip joint, 2: Inability to flex knee joint, 3: Inability to flex ankle) every 2 min till score 3 was attained; then every 15 min till resolution of the block. Motor block assessment was withheld during surgery. Peak sensory level, onset of sensory block (time from intrathecal injection to peak sensory level), duration of sensory block (time taken for regression of the sensory block from the peak sensory level to S1), onset of motor block (time from intrathecal injection to modified Bromage score 3), duration of motor block (time taken for regression of the motor block from score 3 to 0), and pain free period (time from intrathecal injection to first request of analgesia) were recorded. Apgar score at 1 and 5 min, and perioperative side effects including hypotension, bradycardia, nausea, vomiting, sedation, pruritus, respiratory depression and dissociative manifestations as dizziness, delirium, or nystagmus were recorded. Hypotension was defined as MAP <20% of baseline values or systolic blood pressure <100 mmHg and was managed with increasing the rate of IV fluids and administration of ephedrine 3 mg IV, repeated as necessary. bradycardia was defined as HR <60/min and was treated with atropine sulfate 0.6 mg IV. Vomiting was treated with ondansetron 4 mg IV. Sedation was assessed every 15 min intra-operatively, then every 1 h during the first postoperatively for 12 h using a four-point scale (1: Awake, 2: Drowsy but responsive to verbal stimulus, 3: Drowsy but responsive to physical stimulus, 4: Unresponsive to verbal and physical stimulus). Respiratory depression was defined as a respiratory rate ≤10/min.

Patients' satisfaction with anesthesia was evaluated on arrival to the postanesthetic care unit using a visual analogue scale (VAS) with "dissatisfied" at 0 cm and "very satisfied" at 10 cm. Patients in group KMB were followed for 6 months as outpatients in order to assess any neurological disorder.

Statistical analysis

The primary outcome measures were hemodynamic variables and pain-free period. Assuming 40% reduction in frequency of hypotension and 50% increase in pain free period by adding ketamine and midazolam intrathecally to bupivacaine based on results of a previous trail,[9] a sample size of 20 patients in each group was calculated assuming a two-tailed α value of 0.05 and power of 95%. After estimation of a dropout rate of 20%, 25 patients were included in each group. Data were presented as mean (M) ± standard deviation, median (range), or number (%) where appropriate. Patients' and anesthetic characteristics were compared using an independent samples *t*-test. The number of patients with previous CS and side-effects were compared using Fisher's exact test. Patients' satisfaction scores were compared between groups by Mann–Whitney U-test. Independent samples *t*-test was used for comparison of HR and MAP between groups and repeated measures ANOVA test was used to examine the difference in HR and MAP between different times within the same group. $P < 0.05$ was considered as significant.

Results

50 parturients were recruited and completed the study protocol. The patients' characteristics were comparable [Table 1]. The anesthetic characteristics are shown in Table 2; all patients attained a sensory level ≥T8 and a modified Bromage score of 3. There was a statistically significant difference between groups in the peak sensory level ($P = 0.006$), sensory ($P = 0.001$) and motor ($P = 0.005$) onsets, sensory ($P = 0.008$) and motor ($P = 0.002$) block durations, and pain free period ($P = 0.002$). Apgar scores at 1 and 5 min were comparable in both groups ($P = 0.699$ and 0.646 respectively). Six patients in group FB required supplemental fentanyl after exteriorization of the uterus. Patients' satisfaction scores were significantly higher in group KMB ($P = 0.001$).

Heart rate decreased significantly in both groups compared to preblock values ($P = 0.001$ for all comparisons). After intrathecal injection, there was a statistically significant decrease in HR in group FB compared to group KMB at 10 min ($P = 0.001$), 15 min ($P = 0.001$), 20 min ($P = 0.001$), 25 min ($P = 0.010$), 30 min ($P = 0.006$), 45 min ($P = 0.006$), 60 min ($P = 0.017$), and 4 h ($P = 0.003$); [Figure 1]. MAP decreased significantly in both groups compared with the preblock values ($P = 0.001$ for all comparisons). At 5 min ($P = 0.001$) and 10 min ($P = 0.001$), MAP was significantly higher in group KMB compared to group FB [Figure 2]. SpO_2 showed no statistically significant changes ($P > 0.05$ for all comparisons).

Incidences of hypotension ($P = 0.002$), bradycardia ($P = 0.013$) and vomiting ($P = 0.019$) were significantly lower in group KMB. There was no significant difference in the incidences of nausea ($P = 0.500$) and pruritus ($P = 0.245$). Two patients had a sedation score of 2 in the KMB group ($P = 0.245$); [Table 3]. No patients in group KMB reported any sensory or motor deficit during the 6 months follow-up period.

Table 1: Patients' characteristics

Variable	Group KMB (*n* = 25)	Group FB (*n* = 25)	*P*
Age (years)	29.7±3.8	28.5±4.5	0.333
Height (cm)	169.2±4.7	171.2±5.6	0.169
Weight (kg)	86.1±5.3	85.6±3.6	0.665
Gestational age (week)	37.3±1.1	37.6±1.1	0.305
Previous CS (*n* [%])	23 (92)	18 (72)	0.069
Duration of surgery (min)	70.1±5.8	72.4±6.2	0.194

n = Number, CS = Cesarean section, FB = Fentanyl-bupivacaine, KMB = Ketamine-midazolam-bupivacaine

Table 2: Anesthetic characteristics

Variable	Group KMB (*n* = 25)	Group FB (*n* = 25)	*P*
Sensory level[a]	T6 (4-8)*	T8 (4-9)	0.006
Sensory onset (min)	6.08±1.15*	7.36±1.32	0.001
Sensory duration (min)	141.4±18.4*	127.8±16.7	0.008
Motor onset (min)	8.2±1.4*	9.4±1.5	0.005
Motor duration (min)	156.4±21.8*	138.6±17.4	0.002
Pain free period (min)	435±60.3*	362.9±90.5	0.002
Apgar score at 1-min	7.6±1.6	7.7±1.3	0.699
Apgar score at 5 min	9.3±0.6	9.2±0.6	0.646
Patients' satisfaction VAS	9±0.7*	8±1.2	0.001

[a]*Presented as median (range), *Statistically significant difference (P < 0.05), VAS = Visual analogue score, FB = Fentanyl-bupivacaine, KMB = Ketamine-midazolam-bupivacaine*

Discussion

The results of this study suggest that the combination of low-dose ketamine with midazolam and low-dose bupivacaine leads to reductions in hypotension and bradycardia during spinal anesthesia for CS and prolongation of the pain-free period. The combination provided adequate surgical analgesia without significant adverse effects or any effetcs on neonate.

Various investigators,[7,8] showed that intrathecal ketamine (0.1 mg/kg) and midazolam (0.02 mg/kg) with bupivacaine

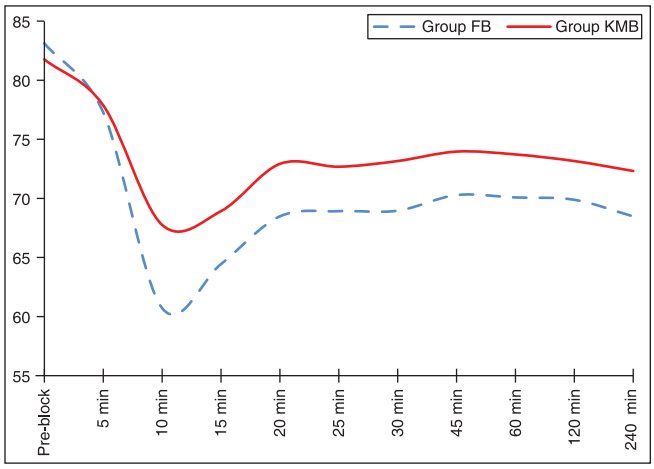

Figure 1: Heart rate at different points in time

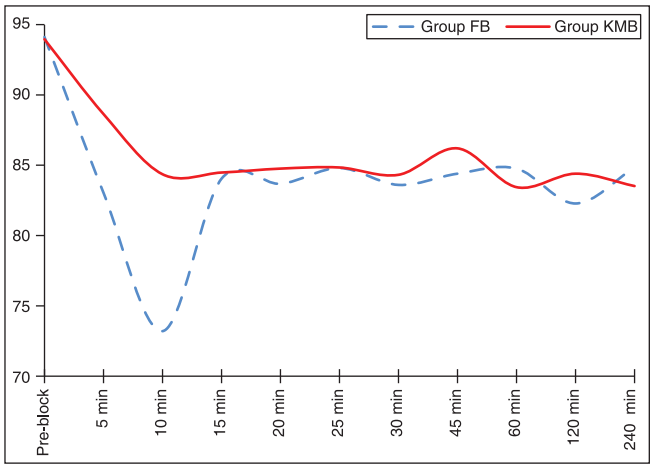

Figure 2: Mean arterial blood pressure at different points in time

(15 mg) stabilizes hemodynamics and prolongs postoperative analgesia without adverse effects. Use of ketamine as an adjuvant to the local anesthetic during spinal anesthesia for CS has been shown to reduce hemodynamic fluctuations and to have a local anesthetic sparing effect.[5,6,9] Ketamine may diffuse into the venous system of the spinal cord and result in cardiovascular stimulation that antagonize spinal anesthesia induced vasodilatation.[10] On the contrary, Unlugenc *et al.*[11] demonstrated that intrathecal low-dose S(+) ketamine (0.05 mg/kg) with bupivacaine (10 mg) for CS did not affect hemodynamics, though it enhanced segmental spread and shortened the onset of anesthesia. Togal *et al.*[12] observed that ketamine (0.1 mg/kg) and bupivacaine (7.5 mg) had no effect on arterial blood pressure and sensorimotor blockade characteristics in elderly patients.

Spinal midazolam has been studied extensively; it enhances sensorimotor blockade and lengthens analgesia without affecting the hemodynamics.[7,13,14] Previous studies[5,14] agree that 1-2 mg intrathecal midazolam is safe and efficacious. Prakash *et al.*[14] showed no differences in arterial blood pressure and HR between patients who received bupivacaine and those who received either 1 mg or 2 mg midazolam with bupivacaine. The duration of postoperative analgesia determined by request for rescue medication was 6.1 ± 1 h in patients administered midazolam 2 mg. On the other hand intrathecal ketamine has been shown to be associated with short lived postoperative analgesia.[5,6] Although it is difficult to differentiate between the analgesic effects of ketamine and midazolam in the present study, intrathecal co-administration of both drugs probably acted in synergy that increased clinical benefits.[7,8] Ketamine has a local anesthetic activity and an analgesic effect mediated through noncompetitive inhibition of N-methyl D-aspartate receptors and binding to opiate receptors in the spinal cord,[13] while the analgesic effect of midazolam is thought to be mediated through binding to specific benzodiazepine receptors.[3,15]

Table 3: Side effects

Variables	Group KMB (n = 25) (%)	Group FB (n = 25)	P
Hypotension	6 (24)*	18 (72)	0.002
Bradycardia	3 (12)*	11 (44)	0.013
Nausea	4 (16)	3 (12)	0.500
Vomiting	2 (8)*	9 (36)	0.019
Sedation	2 (8)	0	0.245
Pruritus	0	2 (8)	0.245

**statistically significant difference ($P < 0.05$), FB = Fentanyl-bupivacaine, KMB = Ketamine-midazolam-bupivacaine*

Decreasing the dose of intrathecal local anesthetics may reduce hemodynamic fluctuation, but may increase the frequency of visceral pain. Visceral pain commonly seen with exteriorization of uterus, is often associated with autonomic activity causing nausea, vomiting, sweating with changes in blood pressure and HR.[16] Addition of fentanyl to low-dose bupivacaine can improve the quality of analgesia, only in doses of 40 μg or greater during CS. However, pruritus has been shown to increase by 50% with fentanyl >35 μg. This is distressing for many patients and is a limiting factor for increasing the dose of intrathecal fentanyl.[17] In the present study, no patients complained of intra-operative pain in the KMB group compared to 6 (24%) patients in the fentanyl-bupivacaine group; also, the incidence of vomiting was significantly lower with the former, probably due to adequate analgesia and less hemodynamic fluctuations. This may explain the higher patients' satisfaction scores.

The limitations of the present study include the ketamine-related dissociative adverse effects such as salivation, dizziness, delirium, and sedation,[5,6] in addition to a concern about the neurotoxicity of intrathecal ketamine[18] and midazolam[19]. However, dissociative manifestations were reported with the

intrathecal ketamine doses ≥25 mg and have been shown to be dose-dependent;[6,11,12] while the neurotoxicity was associated with prolonged and continuous administration.[20] Intrathecal midazolam, even with continuous use, did not result in toxic effect on nerve roots.[21] Tucker *et al*.[22] reported that a 1-week and 1-month postoperative follow-up showed no sign of increased risk of neurologic symptoms in patients who recieived 2 mg midazolam intrathecally compared to those who did not. In the present study, none of the patients who received midazolam and ketamine showed behavioral, psychomimetic, or neurological complications within the 6 months follow-up period.

Conclusion

Intrathecal low-dose ketamine combined with midazolam and low-dose bupivacaine for CS stabilizes hemodynamics and prolongs postoperative analgesia without significant side effects. Further studies are required to prove the safety of such a combination.

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