

Effect of Midazolam on Bupivacaine Action in Intrathecal Anesthesia

Anas Amer M. Ajam, Ramadhan Jaafer Guri¹

Department of Anesthesia, College of Medicine, University of Duhok, ¹Department of Anesthesia, Maternity Teaching Hospital, Duhok, Kurdistan, Iraq

Abstract

Background: Subarachnoid anesthesia is regarded as one of the famous neuroaxial block procedures available nowadays. Neuraxial anesthesia offers many benefits over general anesthesia. **Objective:** This study is designed to compare the effect of adding 1 and 2 mg midazolam to hyperbaric bupivacaine on duration of sensory and motor block and intraoperative hemodynamic changes for the cesarean section under subarachnoid anesthesia. **Methods:** Ninety patients with the American Society of Anesthesiology Classifications I/II (range: 18–40 years) were randomly allocated into three groups and were underwent spinal anesthesia for Cesarean Section in Duhok Maternity Hospital, Iraq. Group A ($n = 30$) received intrathecal of bupivacaine 12.5 mg + 0.4 ml of normal saline, Group B ($n = 30$) intrathecal of bupivacaine 12.5 mg + 1 mg midazolam, and Group C ($n = 30$) intrathecal of bupivacaine 12.5 mg + 2 mg midazolam. The study groups were comparable in age and hemodynamic status changes prior and intra-intervention commencement. **Results:** The analgesic duration of those patients in Groups C and B were significantly longer, 183.33 and 181.00 min compared to 138.00 min in Group A for motor block ($P < 0.0001$) and 212.00, 210.00, and 142.00 min, respectively, for sensory block ($P < 0.0001$) with no any substantial difference in hemodynamic status changes. **Conclusion:** The longer duration of analgesic was found using midazolam adjuvant with bupivacaine compared to free adjuvant group in women underwent spinal anesthesia.

Keywords: Adjuvant, hyperbaric bupivacaine, midazolam, subarachnoid anesthesia

INTRODUCTION

Subarachnoid anesthesia is regarded as one of the famous neuraxial block procedures available nowadays. Subarachnoid anesthesia offers many benefits over general anesthesia including reducing intraoperative loss of blood, decreasing the postoperative incidence of thromboembolic phenomena, and decreasing pain in the early period postoperatively. Spinal anesthesia delivers sufficient anesthesia for undergoing cesarean section patients.^[1,2]

Midazolam is belongs to the benzodiazepine group and works through gamma-aminobutyric acid (GABA) neurotransmitter. It is a drug used for anesthesia, sedation, sleep disturbances, and severe agitation, and it works by making people sleepy, decreasing anxiety, and ability loss to create new memories. It is also beneficial for the management of convulsions. Midazolam can be given orally, intravenously, intramuscular, sprayed into the nose, or in the cheek.^[1,3,4]

Midazolam with 0.5% hyperbaric bupivacaine is used for increasing the duration of subarachnoid anesthesia. *In vitro* by autoradiography has detected that a high concentration of benzodiazepine (GABA-A) receptors is found in the Lamina II of the dorsal horn in the spinal cord of the human being, advocating a potential job in pain regulation.^[5]

Till now, multiple studies on animals have discovered that there is no destruction to the meninges, spinal cord, or nerve roots and *in vitro* studies advocated that clinically beneficial doses of subarachnoid midazolam are unusual to be neurotoxic.^[6] Intrathecal anesthesia is generally preferred over general anesthesia in the obstetric cases due to less complications.^[1] Pregnancy lead to changes in the intraabdominal pressure and effects of hormones which increase the sensitivity of pregnant

Address for correspondence: Dr. Anas Amer M. Ajam,
College of Medicine, University of Duhok, Duhok, Kurdistan, Iraq.
E-mail: dr.anasajam@yahoo.com

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woman to local anesthetic drug so the dose of local anesthetic is often reduced up to two-third.^[7]

Pain relief prolongation by many adjuvants such as morphine, fentanyl, ketamine, and midazolam, were examined and investigated by different investigators. However, each of them has its side effects and limitations, and the necessity for alternative manners and medications always exist.^[8-10]

In the present study, we compared the effect of 1 and 2 mg midazolam added to hyperbaric bupivacaine on the duration of sensory and motor block and intraoperative hemodynamic changes for cesarian section (CS) under spinal anesthesia.

MATERIALS AND METHODS

Study design and patients recruitment

Following obtaining Institutional Ethical Clearance from the Local Health Ethics Committee from the General Duhok Directorate of Health and written informed agreement from the patients, 90 pregnant women (Range: 18–40 years) were underwent elective CS were recruited into the study from April 15, 2015 to October 1, 2015.

For this regard, they were underwent spinal anesthesia for the surgery and study purpose. Patients refused to participate, patients with known allergy to local anesthetic drugs, chronic hypertension, and patients were taking antihypertensive drugs during surgery time were excluded from the study.

In a comparative controlled clinical trial in the theaters of Maternity Teaching Hospital in Duhok, Iraq, patients with the American Society of Anesthesiology Classifications (ASA physical status I and II) were randomly classified into following three groups: Group A ($n = 30$), the patients in this group received intrathecal bupivacaine 12.5 mg (2.5 ml) + 0.4 ml of normal saline total volume was 2.9 ml; Group B ($n = 30$), this group received intrathecal bupivacaine 12.5 mg (2.5 ml) + 1 mg (0.4 ml) midazolam total volume was 2.9 ml; and Group C ($n = 30$) received intrathecal bupivacaine 12.5 mg (2.5 ml) + 2 mg (0.4 ml) midazolam total volume was 2.9 ml. The full required information and the explanation regarding the study and procedure were presented to the patients in the preoperative checkup and visit.

Clinical procedure

At entrance to the operation room, intravenous access was initiated with an 18G intravenous cannula in a wide caliber vein at the forearm, and co-loading had been done with prewarmed Ringer's lactate solution 15 ml/kg body weight infused during 15 min.

Through using precise aseptic precautions, a 25G pencil point spinal needle was established into L3–L4 or L4–L5 intervertebral space in midline approach in sitting position, after verifying free flow of cerebrospinal fluid, predetermined 2.9 ml of drug solution was injected. When the injection finished, a small aseptic dressing was utilized and the patients

placed in a supine position with a pillow beneath the neck and head quickly after introducing of subarachnoid medications. Oxygen (2 L/min) was administered during the procedure using nasal cannula. Fluid therapy was done intraoperatively regarding to the patient body weight, intraoperative losses, and vital signs.

Measurement criteria

Datasheet arrangement for preoperative blood pressure and pulse rate (PR) and intraoperative blood pressure and PR every 5-min interval until the end of operation and postoperative to determine the duration of sensory block was assessed by time to first request for analgesia, and duration of motor block was assessed by time to first movement of the lower limbs at the level of hip joints. The data were collected to compare between the duration of sensory and motor blocks among the 3 groups and comparing the intraoperative hemodynamic changes among them.

Moreover, the following parameters were assessed for the study purpose: (a) assessment of duration of sensory block; (b) assessment of duration of motor block; (c) assessment of hemodynamic changes during the operation including heart rate, blood pressures for every 5 min till the end of surgery; (d) episodes of intraoperative hypotension treated by ephedrine in bolus dose of 5 mg (if mean arterial pressure <70 mmHg); and (e) episodes of intraoperative bradycardia treated by atropine in dose of 0.01 mg/kg (if heart rate <50 beat/min).

Randomization and blinding

During subarachnoid block to ensure the blinding, randomly allocated drug containing syringes were arranged and prepared by an anesthesiologist who did not achieve the subarachnoid block or record the intraoperative and postoperative period outcomes. The investigator and anesthesiologist achieving the study will be blinded to the type of the drugs contained in the syringes and the solution for all the three groups.

Statistical analysis

Data were assessed for normality using Shapiro–Wilk test and homogeneity using Bartlett's test for unequal variances. Relative frequencies and differences between categorical variables were calculated by using Fishers' exact test. Mean $\pm$ standard deviation and the mean differences between continuous variables were calculated using one-way ANOVA.^[11]

Tukey's tests were used to precisely determine where the difference in our means exist across all three groups and whether it is significant. Levels of statistical significance for all tests were set at 0.05. All analyses were conducted using the PROC ANOVA procedure in SAS® software (version 9.4, SAS Institute, Cary, NC, USA).

Sample size of 20 patients for each group was determined in considering the mean duration of 130 ± 45 min for Group A in comparison with the possible duration of 180 ± 40 min for Group C and two-sided with the Cohen's effect size of 1.17 and 95 confidence interval through the G * Power 3.1.9 software

(Heinrich, Heine University Dusseldorf, Germany). However, the sample size was extended to 30 for each group due to lost to follow up possibility.

RESULTS

The baseline characteristics of three study groups prior and intra-intervention commencement were compared in Table 1. The mean age of Group A, B, and C were 28.00 ± 5.21 , 29.00 ± 5.66 , and 28.00 ± 5.34 years, respectively, fairly similar among all three groups. As shown in Table 1, systolic blood pressure (SBP), diastolic blood pressure, and PR of patients in Groups A, B, and C were statistically comparable between groups before and during study intervention phases.

Deterioration of patients' hemodynamic status and the need for atropine and/or ephedrine were reported in Table 2. Among all patients, 47 of them showed at least one episode of hypotension (SBP <70 mmHg) intraoperatively requiring a bolus of 5 mg ephedrine administration intravenously with no a substantial difference. In addition, two patients (6.67%) in Group B and three patients (10%) in Group C developed not <1 episode of bradycardia (PR < 50 bpm) requiring administration of 0.01 mg/kg of atropine intraoperatively, a statistically insignificant finding.

Duration of analgesia

The duration of motor block was longer significantly in the Group C received 12.5 mg bupivacaine + 2 mg midazolam (duration: 183.33 ± 32.77 min), compared to only 181 ± 47.66 min in the Group B received 12.5 mg bupivacaine + 1 mg midazolam and 138 ± 50.53 min in the Group A received only 12.5 mg bupivacaine ($P < 0.0001$), as shown in Table 3.

Similarly, the duration of sensory block was significantly longer in the Group C with a mean duration of 212 ± 48.43 min, compared to 210 ± 51.14 min in Group B, and 142 ± 58.93 min in Group A ($P < 0.0001$), these differences were shown in Figures 1 and 2.

Further statistical analyses showed that the anesthesia durations including motor and sensory block of Group C and B were statistically longer than their compartments in the patients of Group A. However, these differences were statistically significant between Groups B and C for motor and sensory block effects as the results of interventions.

DISCUSSION

The authors' aim in conducting the current study was to evaluate the effect of 1 and 2 mg midazolam added to hyperbaric bupivacaine on the duration of motor and sensory block and intraoperative hemodynamic changes for CS under spinal anesthesia. The study showed that the aesthesia duration was statistically longer in those patients underwent 1 and 2 mg midazolam added to hyperbaric bupivacaine in comparison to the patients were underwent intrathecal bupivacaine 12.5 mg + 0.4 ml of normal saline and no substantial difference was found between Groups B and C. In addition, the no substantial differences of hemodynamic changes were found between three groups.

The effect of added midazolam to hyperbaric bupivacaine on longer analgesic duration in patients underwent regional anesthesia has been approved by other researchers across the world as well. For instance, Kim and Lee^[12] randomly allocated 45 patients to three groups, including the control group ($n = 15$) received 1 ml of 0.5% heavy bupivacaine + 0.2 ml of 0.9% saline intrathecally, group BM1 ($n = 15$) received 1 ml of 0.5% bupivacaine + 0.2 ml (1 mg) of 0.5% preservative-free midazolam and group BM2 ($n = 15$) received 1 ml of 0.5% bupivacaine + 0.4 ml (2 mg) of 0.5% midazolam.

First time to rescue analgesic required by the patients was of great significance in the midazolam groups rather

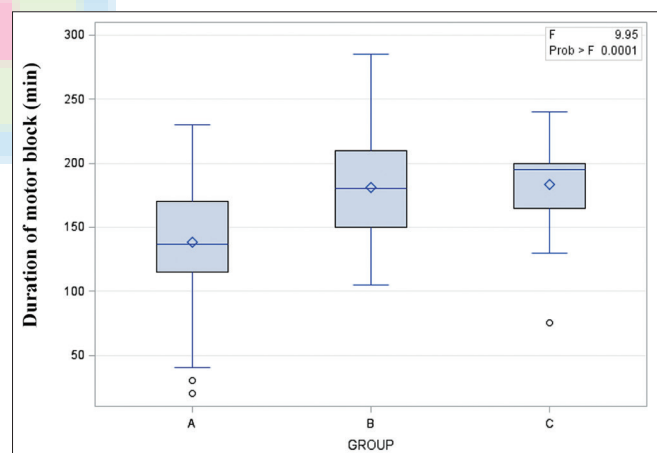


Figure 1: Distribution of motor block duration, $F = F$ test for the ANOVA. Probability > $F = P$ value for the F test significant at a level of 0.05

Table 1: Baseline characteristics of three study groups prior and intra-intervention commencement

Baseline characteristics of patients	Mean $\pm$ SD			P^*
	Group A ($n=30$)	Group B ($n=30$)	Group C ($n=30$)	
Age (years)	28.00 ± 5.21	29.00 ± 5.66	28.00 ± 5.34	0.711
Preoperative SBP (mmHg)	135.30 ± 14.58	137 ± 18.39	130.73 ± 18.52	0.306
Preoperative DBP (mmHg)	80.73 ± 9.47	78.87 ± 15.24	78.70 ± 13.38	0.796
Preoperative PR (bpm)	118.57 ± 15.57	112.90 ± 19.34	107.83 ± 16.86	0.061
Mean intraoperative SBP (mmHg)	115.59 ± 20.37	114.51 ± 14.74	105.63 ± 15.91	0.053
Mean intraoperative DBP (mmHg)	61.40 ± 15.91	57.01 ± 9.27	58.67 ± 18.76	0.531
Mean intraoperative PR (bpm)	108.22 ± 15.64	102.12 ± 15.04	103.64 ± 17.74	0.324

*One-way ANOVA was performed for all statistical differences. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PR: Pulse rate

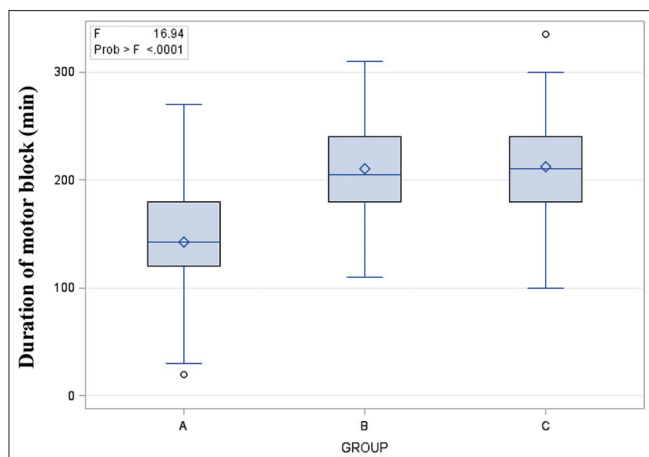


Figure 2: Distribution of sensory block duration, $F = F$ test for the ANOVA. Probability $> F = P$ value for the F test significant at a level of 0.05

Table 2: Intraoperative hemodynamic deterioration by the study group

Hemodynamic aspects	Group A, n (%)	Group B, n (%)	Group C, n (%)	P^*
Bradycardia (required 0.01 mg/Kg atropine)*	0	2 (6.67)	3 (10)	0.360
Hypotension (required 5mg ephedrine intravenously)	12 (40)	14 (46.67)	21 (70)	0.058

*One-sample Fishers' exact test was performed for statistical analysis

Table 3: Duration for motor and sensory block by the study groups following interventions

Duration	Mean $\pm$ SD			P^*
	Group A	Group B	Group C	
Duration of motor block (min)	138.00 $\pm$ 50.53	181.00 $\pm$ 47.66	183.33 $\pm$ 32.73	<0.0001
Duration of sensory block (min)	142.00 $\pm$ 58.93	210.00 $\pm$ 51.14	212.00 $\pm$ 48.43	<0.0001

*One-way ANOVA was performed for statistical analyses. SD: Standard deviation

than in the placebo and with less significance in the BM1 group than in the BM2 group with statistically insignificant difference in hemodynamic change among the 3 groups. Similarly, a meta-analysis confirmed that adding of 1 mg or 2 mg of subarachnoid midazolam will prolong the analgesic effect of bupivacaine postoperatively by approximately 2 h and 4.5 h, respectively, compared with controls group posthemorrhoidectomy advocating a dose-dependent action of subarachnoid midazolam.

However, we should put in our minds that pain of hemorrhoidectomy can be reduced only by blocks of sacral sensory nerves. In this study, patients underwent below umbilical obstetric surgeries, and for adequate analgesia, our patients required blockade of lumbar and lower thoracic dermatomes as well. The similar results were obtained by

Batra *et al.*^[13] without prolonging recovery among patients underwent knee arthroscopy. Even the longer analgesic duration was found by Chattopadhyay *et al.*^[14] in patients underwent spinal analgesia for elective infraumbilical surgery, 320 min in adjuvant group versus 220 min in free midazolam group for sensory block and 255 min versus 195 min for motor block, respectively, and no substantial difference in side effects between both groups.

Shadangi *et al.*^[15] allocated randomly 100 patients into two groups prepared for elective lower abdominal, lower limb, and gynecological procedures in a double-blind way for intrathecal drug administration. They showed the longer duration of sensory block in the midazolam group, 115.8 versus 90.8 min ($P = 0.001$), while in similar with our study, no significant difference was found in motor blockage, 151.3 versus 151.8 min ($P = 0.051$).

The current study was strength in successful randomly and double blind of patients into three study groups. However, the study was not exempt from the limitations. The results reported in the present study must be interpreted in the inherent of study design and take into account the stern exclusion criteria as we did not make a between-group comparison for the interventions side effects (except hemodynamic status) in patients underwent intrathecal bupivacaine 12.5 mg + 1 mg midazolam, and those underwent intrathecal bupivacaine 12.5 mg + 2 mg midazolam. However, it has been reported that 1 and 2 mg intrathecal midazolam is able to decrease postoperative nausea and vomiting,^[16] or make do not significant change.^[15]

CONCLUSION

It is concluded from this study that using of 1 mg midazolam + bupivacaine in comparison with 2 mg midazolam + bupivacaine have the same effect on duration of sensory and motor block with less side effects. Hence, we recommend using of 1 mg midazolam with bupivacaine instead of 2 mg to increase the duration of motor and sensory block during subarachnoid anesthesia for CS.

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Conflicts of interest

There are no conflicts of interest.

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