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Modulation of Bupivacaine-Induced Spinal Anesthesia by Intrathecal Midazolam: A Pharmacodynamic Analysis

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Abstract

Background: Subarachnoid Block remains a widely utilized neuraxial technique in contemporary anesthetic practice, offering distinct clinical advantages compared to general anesthesia. Objective: The present investigation aims to evaluate the impact of incorporating either 1 mg or 2 mg of midazolam adding to hyperbaric bupivacaine upon the sensory and motor blockade durations, as well as intraoperative circulatory fluctuations, during spinal anesthesia for cesarean delivery. Patient and method: A total of 180 parturient, classified according to American Society of Anesthesiologists (ASA) physical status I or II and aged between 18 and 40 years, were distributed randomly in to three groups planned for elective cesarean section under neuroaxial anesthesia (spinal anesthesia) at AL Basra teaching hospital, Iraq. Group Ⅰ (n = 60) received an intrathecal combination comprising 12.5 mg of bupivacaine supplemented with 0.4 ml of isotonic saline, whereas group Ⅱ (n = 60) was administered 12.5 mg of bupivacaine combined with 1 mg of midazolam, and group Ⅲ (n = 60) received 12.5 mg of bupivacaine together with 2 mg of midazolam. The three groups displayed similarity regarding maternal age and baseline hemodynamic parameters, both before and immediately after initiation of the spinal intervention. Results: Patients in Groups Ⅱ and Ⅲ experienced significantly extended pain relief durations, regarding motor block times of 190 and 187 minutes versus 145.00 minutes in Group 1 (P value< 0.0001). Similarly, sensory block durations were 219.00, 217.00, and 149.00 minutes, respectively (P value < 0.0001). No notable variations in hemodynamic stability were observed across the cohorts. Conclusion: Among women receiving spinal anesthesia, combining midazolam as an adjuvant with bupivacaine provides a prolonged analgesic effect compared to using bupivacaine alone without an additive.

Keywords

Additive,
Heavy Bupivacaine,
Midazolam,
Spinal Anesthesia

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Introduction:

Subarachnoid block remains one of the most widely utilized neuraxial techniques in contemporary anesthetic practice. Compared to general anesthesia, spinal anesthesia confers several clinical advantages, such as diminished perioperative hemorrhage, a lower postoperative risk of thromboembolic events, and improved early postoperative pain control. In particular it provides adequate surgical anesthesia [1].

Midazolam, a benzodiazepine derivative, exerts its effects via modulation of the gamma-aminobutyric acid (GABA) system. This agent is indicated for induction of anesthesia, procedural sedation, management of insomnia, and control of acute agitation, and it is characterized by sedative, anxiolytic, and anterograde amnestic properties. Additionally, it is effective in the treatment of seizure activity. Midazolam may be administered through various routes, including oral, intravenous, intramuscular, intranasal, or buccal delivery. [3] Intrathecal administration of midazolam as an adjuvant to 0.5% hyperbaric bupivacaine has been shown to prolong the duration of spinal anesthesia. Experimental auto radiographic studies have demonstrated a high density of γ-aminobutyric acid type A (GABA-A) benzodiazepine receptors within lamina II of the dorsal horn of the human spinal cord, suggesting that these receptors play an important role in modulating nociceptive transmission and spinal analgesia [4].

Evidence from numerous animal experiments has consistently shown that injection of midazolam in to the subarachnoid space does not produce neural structural damage regarding spinal cord, meninges, or nerve roots. Furthermore, laboratory investigations indicate that the doses of intrathecal midazolam commonly used in clinical practice are unlikely to exert neurotoxic effects, supporting its safety profile when administered in appropriate therapeutic concentrations. [3] .

For obstetric procedures, spinal anesthesia remains the anesthetic technique of choice for multiple reasons it is associated with fewer maternal and fetal complications than general anesthesia [1] . Physiological adaptations during pregnancy, including elevated intra-abdominal pressure and hormonal changes, increase the susceptibility of pregnant women to the effects of local anesthetic agents, thereby enhancing the characteristics of neuraxial blockade.

Materials and Methods

The study done within the operating suites in AL Basra Teaching Hospital, Iraq, from April 15, 2016 to 15 October 2017 all patient classifies according to the American Society of Anesthesiologists (ASA) physical status as Class I or II. Then distributed randomly to one of three equal cohorts (n = 60 per group):

- Group Ⅰ: Administered a spinal injection containing 12.5 mg (2.5 mL) of bupivacaine supplemented with 0.4 mL of normal saline, yielding a cumulative volume of 2.9 mL.
- Group Ⅱ: Administered an intrathecal regimen of 12.5 mg (2.5 mL) bupivacaine combined with 1 mg (0.4 mL) of midazolam, totaling 2.9 mL in volume.
- Group Ⅲ: Received a subarachnoid mixture of 12.5 mg (2.5 mL) bupivacaine plus 2 mg (0.4 mL) of midazolam, reaching a total volume of 2.9 mL.

Clinical Procedure:

After the patients arrived in the operating theater, peripheral venous access was established using an 18-gauge intravenous

catheter inserted into a large vein of the forearm. Simultaneously, a co-loading regimen consisting of warmed Ringer's lactate solution at a dose of 15 mL/kg was administered over approximately 15 minutes. Under strict sterile conditions, spinal anesthesia was performed with the patient in the sitting position. A 25-gauge pencil-point spinal needle was introduced via the midline approach into either the L3–L4 or L4–L5 intervertebral space. Once clear cerebrospinal fluid was obtained, a total of 2.9 mL of the prepared anesthetic solution was injected intrathecally.

Following needle withdrawal, the puncture site was covered with a sterile dressing and immediately following the subarachnoid injection, patients were placed flat on their backs with a pillow supporting the head and neck. Supplemental oxygen was delivered throughout the procedure via nasal cannula at a rate of 2 L/min. Intravenous hydration was adjusted during surgery based on individual body weight, fluid losses, and physiological parameters. Preoperative and intraoperative hemodynamic measurements—including arterial blood pressure and heart rate—were recorded at 5-minute intervals until the end of operation.

Postoperatively, sensory block persistence was evaluated based on the time elapsed before the patient requested their initial dose of pain relief. Motor block regression was determined by measuring the time until active movement was restored at the hip joints. These metrics were gathered to compare sensory and motor block durations as well as cardiovascular stability across the three study cohorts. For the purposes of this investigation, the following outcome measures were recorded: duration of persistence sensory and motor block.

fluctuations of circulatory parameter regarding pulse rate and arterial pressure readings, documented at five-minute intervals until surgical completion;
(4)attacks of blood pressure reduction (mean below 60mmhg) during surgery that required management with 5-mg intravenous pushes of ephedrine,
(5) attacks of heart rate reduction (pulse rate below 50 bpm) during operation that necessitated intervention with atropine at a dosage of 0.01 mg/kg body weight .

To maintain allocation concealment during the administration of spinal anesthesia, all study medications were prepared in identical syringes by an independent anesthesiologist who was not involved in performing the subarachnoid block or collecting intraoperative and postoperative data. Both the investigator and the anesthesiologist responsible for administering the spinal anesthesia remained unaware of the treatment assignment throughout the study. Consequently, the identity of the drug solutions administered to participants in all three study groups was concealed until completion of data collection.

Statistical Analysis

The distribution of continuous variables was evaluated using the Shapiro–Wilk test to determine normality, while Bartlett's test was applied to assess the equality of variances among the study groups. Categorical variables were summarized as frequencies and percentages, and comparisons between groups were performed using Fisher's exact test. Continuous data were expressed as the mean, and intergroup differences were analyzed using one-way analysis of variance (ANOVA).

Results

Preoperative and intraoperative baseline parameters across the three cohorts are outlined in Table 1. Age distributions were comparable among the arms, with mean values recorded at 28.00 ± 5.21 years for Group Ⅰ, 29.00 ± 5.66 years for Group Ⅱ, and 28.00 ± 5.34 years for Group Ⅲ. Likewise, initial and ongoing measurements of systolic blood pressure (SBP), diastolic blood pressure, and pulse rate (PR) showed no statistically significant discrepancies between the study arms throughout the intervention period (Table 1).

Hemodynamic instability and the required therapeutic interventions are detailed in Table 2. Across the total sample, 47 subjects experienced at least one intraoperative hypotensive event SBP < 75 mmHg, which was managed via intravenous administration of a 5 mg ephedrine bolus, displaying no meaningful variance between groups. Additionally, intraoperative bradycardia PR < 50 bpm occurred in two patients (6.67%) in Group Ⅱ and three patients (10%) in Group Ⅲ, requiring 0.01 mg/kg of intravenous atropine; this variance was statistically insignificant. As detailed in Table 3, motor block persistence was significantly prolonged in Group Ⅲ 12.5 mg bupivacaine combined with 2 mg midazolam, averaging *190.33 ± 32.77* minutes. In comparison, Group Ⅱ (12.5 mg bupivacaine with 1 mg midazolam) recorded a duration of *188.00 ±47.66* minutes, while Group Ⅰ (12.5 mg bupivacaine alone) demonstrated a noticeably shorter duration of *145.00 ± 50.53* minutes (P value < 0.0001).

The average length of sensory blockade in Group Ⅲ was 219 ± 48.43 minutes, which was notably greater than the 217 ± 51.14 minutes observed in Group Ⅱ and the 149 ± 58.93 minutes recorded for Group Ⅰ (P < 0.0001). Additional testing revealed that both motor and sensory blockade periods in Groups Ⅱ and Ⅲ were substantially extended relative to those in Group Ⅰ. Nevertheless, when comparing Groups Ⅱ and Ⅲ directly, the variations in both motor and sensory blockade durations reached statistical significance, indicating a clear effect of the administered interventions.

Table 1: Basic inter group demographic data

Baseline characteristics of patients	Group Ⅰ (n=60) Mean ±SD	Group Ⅱ (n=60) Mean ±SD	Group Ⅲ (n=60) Mean ±SD	P value
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	0.796
Preoperative DBP (mmHg)	80.73±9.47	78.87 ±15.24	78.70±13.38	0.061
Preoperative PR (bpm) Mean	112.57±13.5	106.90±17.3	101.83±14.8	0.053

Table 2: intergroup comparison of Hemodynamic Instability.				
Hemodynamic aspects	Group Ⅰ n =60	Group Ⅱ n =60	Group Ⅲ n=60	P value
Bradycardia (required 0.01 mg/Kg atropine)	0	2	3	0.360
Hypotension (required 5mg ephedrine intravenously)	14	16	23	0.058

Table 3: Motor and Sensory Block Durations Among the Treatment Groups.				
Duration	Group Ⅰ mean	Group Ⅱ mean	Group Ⅲ mean	P value
Duration of motor block (min)	145.00 ± 50.53	188.00 ±47.66	190.33 ± 32.77	<0.0001
Duration of sensory block (min)	149.00 ±58.93	217.00 ±51.14	219.00 ±48.43	<0.0001

Discussion:

The primary objective of this investigation was to assess how supplementing hyperbaric bupivacaine with 1 mg or 2 mg of midazolam influences motor and sensory block durations, as well as cardiovascular stability, during spinal anesthesia for cesarean section delivery. Findings revealed that incorporating midazolam (either 1 mg or 2 mg) into hyperbaric bupivacaine significantly extended the overall anesthetic duration compared to the control regimen of 12.5 mg intrathecal bupivacaine plus 0.4 mL normal saline.

However, no statistically significant difference in block prolongation was observed between Groups Ⅱ and Ⅲ. Furthermore, hemodynamic parameters remained well-preserved, exhibiting no meaningful variation across the three intervention arms. The ability of midazolam adjuvants to prolong regional pain relief alongside hyperbaric bupivacaine aligns with conclusions reached by investigators globally. As an illustration, Kim and Lee [6] randomly assigned 45 subjects into three equal cohorts (n = 15 per group): a control cohort receiving a subarachnoid injection of 1 mL 0.5% heavy bupivacaine combined with 0.2 mL 0.9% saline; group BM1 receiving 1 mL 0.5% bupivacaine plus 0.2 mL (1 mg) 0.5% preservative-free midazolam; and group BM2 receiving 1 mL 0.5% bupivacaine plus 0.4 mL (2 mg) 0.5% midazolam.

The initial requirement for rescue analgesia in patients was notably more critical in the midazolam cohorts relative to the placebo arm, with this effect being less pronounced in the BM1 subset compared to the BM2 subset, though variations in hemodynamic parameters across all three study arms did not reach statistical significance. In parallel, a pooled analysis of prior trials has demonstrated that the inclusion of either 1 mg or 2 mg of intrathecal midazolam extends the postoperative duration of bupivacaine

analgesia by roughly 2 hours and 4.5 hours, respectively, relative to control groups following hemorrhoidectomy, thereby supporting a dose-dependent mechanism for spinal midazolam. Nonetheless, it must be recognized that post-hemorrhoidectomy discomfort can be effectively mitigated solely through sacral sensory nerve blockade. In the present investigation, however, participants underwent obstetric procedures below the umbilicus, necessitating blockade of both lumbar and lower thoracic dermatomal levels to achieve satisfactory pain control. Comparable findings have been reported in earlier work. Batra et al. [7].without delaying patient recovery following knee arthroscopy.

Similarly, Chattopadhyay et al. [8] demonstrated extended pain relief in individuals receiving spinal block for elective infraumbilical procedures, reporting sensory block durations of 320 minutes in the adjuvant cohort compared to 220 minutes in the bupivacaine-only cohort, along with motor block durations of 255 minutes versus 195 minutes, respectively; importantly, adverse event rates did not differ significantly between the two groups.

In a double-blind design, Shadangi et al. [9] randomly assigned 100 candidates scheduled for elective gynecological, lower limb, or lower abdominal operations into two treatment arms to assess intrathecal drug administration. The midazolam cohort exhibited a markedly extended sensory blockade duration, averaging 115.8 minutes compared to 90.8 minutes in the control group ($P = 0.001$). In alignment with our observations, motor blockade duration showed no notable disparity, recorded at 151.3 versus 90.8 minutes ($P = 0.051$). A key strength of this investigation lies in the effective randomization and double-blinding applied across the three patient groups. We did not perform comparative analyses between the intervention arms regarding adverse effects (apart from hemodynamic parameters) for participants receiving intrathecal bupivacaine 12.5 mg combined with either 1 mg or 2 mg of midazolam. That said, prior evidence indicates that intrathecal midazolam at doses of 1 and 2 mg may reduce postoperative nausea and vomiting, [10] or alternatively, produce no substantial effect. [9].

Conclusion

This investigation demonstrates that combining 1 mg of midazolam with bupivacaine yields analgesic and motor block durations equivalent to those achieved with a 2 mg dose, while incurring a lower incidence of adverse effects. Consequently, the lower 1 mg midazolam dose is advised as an optimal additive to bupivacaine for extending sensory and motor blockade in women undergoing cesarean delivery under spinal anesthesia.

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