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Original Research

To compare the effectiveness and safety of combining intrathecal midazolam with bupivacaine with using bupivacaine alone in subarachnoid block for cesarean delivery

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ABSTRACT:

Aim: To compare the effectiveness and safety of combining intrathecal midazolam with bupivacaine with using bupivacaine alone in subarachnoid block for cesarean delivery. **Material and methods:** This research included pregnant women between the ages of 20 -40 who were scheduled for an elective Caesarean section and had an ASA grade of I or II. A comprehensive history was acquired and a meticulous general and systematic evaluation was conducted. A preoperative assessment was conducted one day before the procedure. Prior to surgery, patients had a comprehensive evaluation for systemic disorders and underwent laboratory investigations including complete blood count (CBC), urine routine and microscopic inspection, kidney function tests (KFT), liver function tests (LFT), and blood sugar level (BSL) assessment. The process of administering spinal anesthesia was described to the patients, and their signed agreement was acquired. Patients were randomly divided into group B and group BM by chit method. The B group received 10 mg bupivacaine intrathecally. BM group received 10 mg bupivacaine combined with 2 mg of preservative-free midazolam intrathecally. **Results:** The baseline maternal parameters, including age, weight, height, pulse rate, systolic blood pressure, and diastolic blood pressure, were similar in both groups, and the difference was not statistically significant. The duration of the procedure was similar in both groups. Group BM exhibited an early start of sensory and motor block, together with an extended duration of sensory and motor block and effective analgesia, in comparison to group B. This difference was shown to be statistically significant. There were no instances when a patient did not respond well to a spinal block. The current investigation observed complications including bradycardia, hypotension, nausea, and vomiting. Group B exhibited a higher incidence of bradycardias and hypotension, while experiencing a lower occurrence of nausea/vomiting compared to group BM. However, this difference did not reach statistical significance. In the current investigation, no instances of respiratory depression, partial block, or pruritus were observed. **Conclusion:** The use of intrathecal midazolam with bupivacaine decreases the time it takes for sensory and motor block to occur, greatly extends the duration of pain relief, and does not lead to an increase in problems among patients having cesarean birth.

Keywords: Intrathecal midazolam, Bupivacaine, Subarachnoid block, Cesarean delivery

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INTRODUCTION

There has been a significant rise in the frequency of cesarean sections seen in both industrialized and developing nations [1]. Spinal anesthesia is the recommended method of regional anesthesia for cesarean delivery. The primary constraints of spinal anesthesia are its limited duration of effect and its inability to provide extended postoperative pain relief when administered alone with local anesthetics. The addition of adjuvant medications to intrathecal local anesthetics enhances the effectiveness and duration of spinal blockade, as well as extends postoperative pain relief [2]. The Sub-Arachnoid Block is the ideal method for performing a cesarean section because to its advantages of being simple, dependable, and having low rates of airway difficulties and aspiration. Additionally, it allows the woman to remain awake throughout the delivery, which promotes bonding

between the mother and newborn and facilitates effective nursing. Nevertheless, this surgery offers only a limited period of pain relief and might lead to maternal hypotension during the perioperative period, which may have harmful effects. The administration of a local anesthetic during neuraxial blockade has been identified as the cause of hypotension in a way that is dependent on the dosage. Reducing the dosage of local anesthetic reduces the severity of low blood pressure but may undermine the effectiveness of anesthesia. Intrathecal adjuvants have a beneficial impact by enhancing the action of local anesthetics. This allows for reducing the amount of local anesthetic used, which in turn decreases the occurrence of low blood pressure without affecting the effectiveness of anesthesia. In addition, by extending the length of time that pain relief is provided, they provide a painless period after surgery, which is particularly beneficial after a cesarean section, allowing new moms to attend to and form a connection with their newborns [3]. A Caesarean section requires a significant degree of sensory block at the T4 level, which in turn necessitates a substantial dosage of bupivacaine, a local anesthetic. However, it is important to note that bupivacaine may cause side effects like hypotension, nausea and vomiting, as well as a protracted recovery period after the operation. Bupivacaine is the predominant medicine used for spinal anesthesia, with a duration of action ranging from 75 to 150 minutes. Providing quick and efficient pain relief is always difficult, but it is crucial for reducing the body's reactions to pain, such as hormonal and metabolic changes after surgery, reflexes that negatively affect organ function, muscular spasms, and other unwanted outcomes [4]. The identification of different spinal receptors such as 2-adrenergic, cholinergic, opioid, N-methyl-D-aspartate, gamma-aminobutyric acid (GABA), and benzodiazepine receptors has led to the utilization of drugs like clonidine, neostigmine, opioids, ketamine, and midazolam to enhance the pain-relieving effects of hyperbaric bupivacaine (0.5%) and prolong the duration of analgesia [5]. Benzodiazepines are typically used for the purpose of reducing anxiety, inducing forgetfulness, and promoting drowsiness. The identification of benzodiazepine receptors in the spinal cord prompted the use of intrathecal midazolam for pain relief. Multiple studies have shown that the introduction of midazolam by intrathecal or epidural routes results in a dose-dependent adjustment of spinal nociceptive processing in both animals and people. Furthermore, this administration method is not linked to any harmful effects on the nervous system, respiratory function, or sedation. Several studies have assessed the efficacy of intrathecal midazolam for post-operative pain relief in cesarean patients without complications [6,7]. The purpose of this research was to assess the practicality of reducing the amount of bupivacaine used for sub-arachnoid block in order to decrease the occurrence of low blood pressure, while also extending the duration of pain relief by introducing midazolam.

MATERIAL AND METHODS

The research was carried out at the anesthesiology department, M L B Medical College Jhansi over a period of 1 year. The research design included a hospital-based comparative, interventional approach. The study obtained permission from the institutional ethics committee. This research included pregnant women between the ages of 20 -40 who were scheduled for an elective Caesarean section and had an ASA grade of I or II. Patients with adverse obstetric history, concurrent medical conditions during the current pregnancy including hypertension, cardiac illness, renal disease, and liver disease, as well as individuals with mental problems, additional administration of general anesthesia during procedure, participants who had contraindications to spinal anesthesia and those who were unwilling to participate in this study were excluded.

METHODOLOGY

A comprehensive history was acquired and a meticulous general and systematic evaluation was conducted. A preoperative assessment was conducted one day before the procedure. Prior to surgery, patients had a comprehensive evaluation for systemic disorders and underwent laboratory investigations including complete blood count (CBC), urine routine and microscopic inspection, kidney function tests (KFT), liver function tests (LFT), and blood sugar level (BSL) assessment. The process of administering spinal anesthesia was described to the patients, and their signed agreement was acquired. Patients were randomly divided into group B and group BM by chit method.

- The B group received 10 mg bupivacaine intrathecally
- BM group received 10 mg bupivacaine combined with 2 mg of preservative-free midazolam intrathecally.

During the surgical procedure, the normal monitoring procedures were performed and the first measurements of the patient's vital signs were recorded. Prior to spinal anesthesia, each patient received a preload of 10 mL/kg of Ringer lactate solution. Spinal anesthesia was administered following strict aseptic measures. During the surgery, the patients' hemodynamic parameters, including the maternal pulse rate, non-invasive blood pressure, oxygen saturation, and breathing rate, were regularly assessed and documented. Conventional postoperative care was administered. The duration of effective pain relief was measured from the moment the medicine was administered intrathecally to the first instance of additional pain medication being given as a backup. Following the surgery, measurements of blood pressure, pulse rate, pain severity, and SPO2 were taken at certain time intervals: 30 minutes, 1 hour, 2

hours, 4 hours, 6 hours, 8 hours, 12 hours, 16 hours, 20 hours, and 24 hours. The study monitored and documented the occurrence of negative outcomes such as low blood pressure, slow heart rate, and decreased breathing.

STATISTICAL ANALYSIS

The data was gathered using a pre-designed form, inputted into Microsoft Excel, and analyzed using SPSS version 25.0. The data of the two groups were compared and represented as the mean plus or minus the standard deviation (mean ± SD). The statistical analysis included the use of Student's paired t-test for quantitative data and the Chi-square test for qualitative factors. A p-value less than 0.05 was deemed to be statistically significant.

RESULTS

A total of 100 pregnant women were included in the trial, with 50 assigned to each group: Group B (10 mg bupivacaine) and Group BM (10 mg bupivacaine mixed with 2 mg of preservative-free midazolam). The baseline maternal parameters, including age, weight, height, pulse rate, systolic blood pressure, and diastolic blood pressure, were similar in both groups, and the difference was not statistically significant.

Table 1 Basic parameter of the participants

	Group B=50	Group BM=50	P value
Age in years			0.16
20-25	28(56%)	27(54%)	
25-30	12(24%	12(24%)	
Above 30	10(20%)	11(22%)	
Mean age	24.27 ± 2.3	25.14 ± 3.5	
Weight (in kgs)	66.4 ± 8.7	66.9 ± 5.7	0.22
Height (in cms)	153.3 ± 7.3	154.5 ± 6.1	0.19
ASA status			0.11
I	35(78%)	32(71%)	
II	10(22%)	13(29%)	
PulseRate(permin)	83.3±12.5	81.6±13.1	0.27
SystolicBP(mmHg)	112.4±15.5	108.3±13.4	0.17
Diastolic BP(mmHg)	73.5±6.2	75.5±7.7	0.15

The duration of the procedure was similar in both groups. Group BM exhibited an early start of sensory and motor block, together with an extended duration of sensory and motor block and effective analgesia, in comparison to group B. This difference was shown to be statistically significant. There were no instances when a patient did not respond well to a spinal block.

Table 2: Comparison of sensory parameters in two groups

Parameter	Group B	Group BM	P value
Duration of surgery(min)	36.55±3.67	37.29±4.69	0.19
Onset of sensory block(min.)	4.56±0.78	2.69±0.66	0.04
Duration of sensory block(min.)	115.38±5.66	137.88±5.99	0.03
Onset of motor block(min.)	5.58±0.87	3.36±0.49	0.043
Duration of motor block(min.)	137.29±4.83	111.13±5.45	0.026
Mean duration of effective analgesia	157.78±6.46	188.98±6.46	0.032

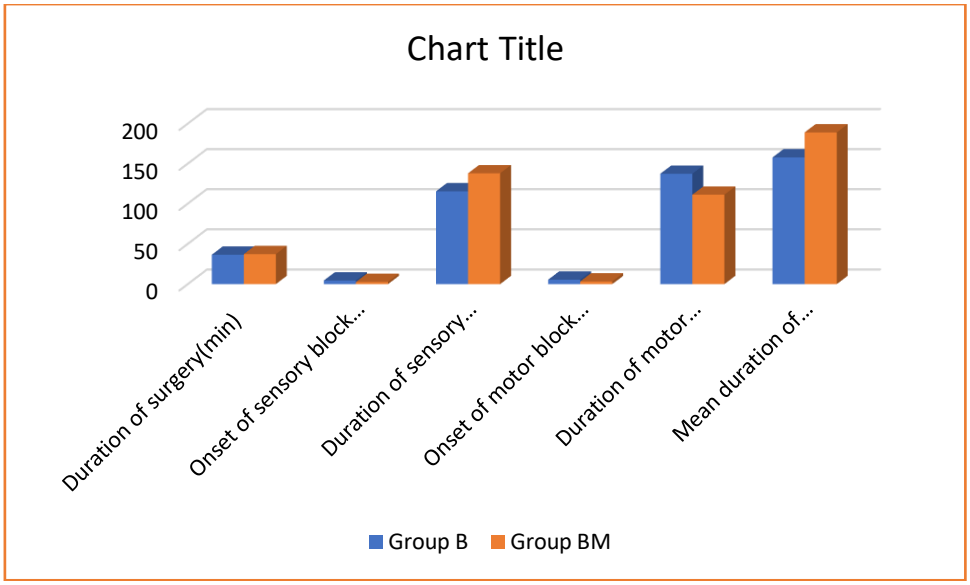

Figure 1: Comparison of sensory parameters in two groups

The current investigation observed complications including bradycardia, hypotension, nausea, and vomiting. Group B exhibited a higher incidence of bradycardias and hypotension, while experiencing a lower occurrence of nausea/vomiting compared to group BM. However, this difference did not reach statistical significance. In the current investigation, no instances of respiratory depression, partial block, or pruritus were observed.

Table 2 Complications in both groups

Complications	Group B=50		Group BM=50		P value
	Number	Percentage	Number	Percentage	
Bradycardia	3	6	2	4	0.11
Hypotension	3	6	2	4	
Nausea and vomiting	2	4	3	6	

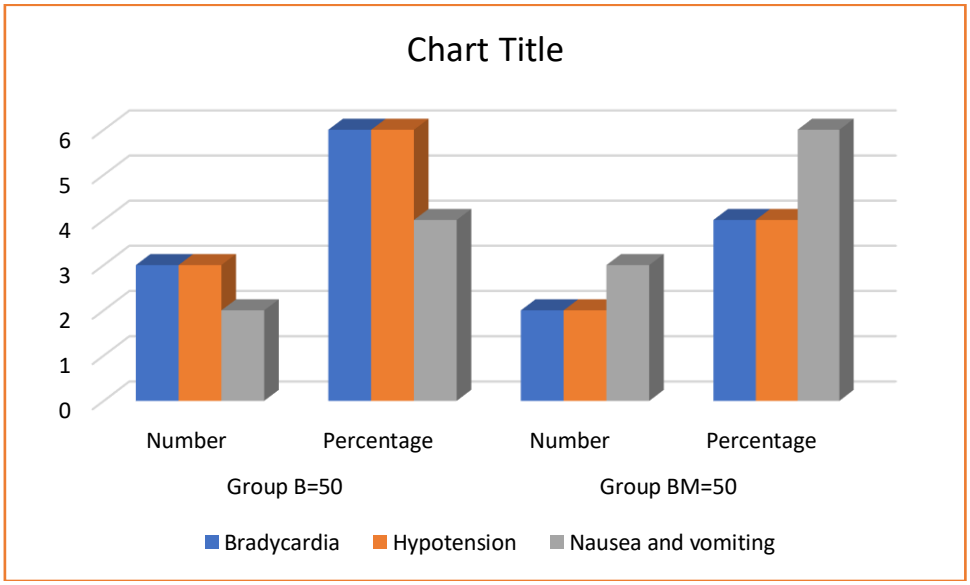

Figure 2: Complications in both groups

DISCUSSION

The sub-arachnoid block is the preferred anesthetic method for cesarean section due to its ease of application, quick onset of effects, the woman's consciousness throughout childbirth, and reduced problems for both the mother and newborn. However, the analgesic effect of this treatment is very temporary and might potentially cause low blood pressure in the mother during the perioperative period, which can be harmful. Reducing the dosage of local anesthetic lessens the severity of low blood pressure but affects the effectiveness of anesthesia. The use of intrathecal

adjuvants, due to their synergistic effect, enables a reduction in the dosage of local anesthetic while extending the duration of pain relief. The gate hypothesis of pain has significantly impacted the anaesthesiologist's approach to pain treatment by directing their attention to the distinctive pharmacology of the dorsal horn of the spinal cord. Anaesthesiologists have acquired the ability to inhibit the transmission of pain signals at the first synaptic connection in the spinal cord by the administration of intrathecal and epidural injections. This approach has significant ramifications in the treatment of both acute and chronic pain. Drugs delivered via the neuraxial route may provide pain relief while minimizing the systemic negative effects associated with intravenous administration. A prevailing contemporary perspective on perioperative pain is to see it as an obstacle to the process of recuperation. Aggressive techniques are often used to reduce discomfort and expedite hospital discharge, allowing for a fast return to regular functional activities. Intrathecal adjuvants are a simple and readily available approach of provide pain relief. Opioids are often used as supplementary medications along with local anesthetics to enhance pain relief during surgery and after the operation. This is achieved by administering 0.5% hyperbaric bupivacaine via the intrathecal channel. Nevertheless, drowsiness, pruritus, urine retention, emesis, and the potential for respiratory depression are the primary considerations associated with opioids. Researchers have discovered that benzodiazepines may selectively block pain signals without causing any harm to the circulatory and respiratory systems, making them a promising option for safer local anesthesia. Benzodiazepines are often not classified as analgesics. Administering these medications by any method that results in elevated drug concentrations in the bloodstream makes it unfeasible to prove the presence of pain-relieving effects beyond their impact on awareness and anxiety. However, the administration of midazolam intrathecally may specifically target the spinal cord, providing access to receptors responsible for pain relief [7,8].

The primary factors contributing to post-operative pain after a cesarean birth are the size and length of the anesthetic block, the discomfort experienced during the removal of the uterus, and the manipulation of other abdominal organs. Administering a high dosage of local anesthetic may enhance the magnitude and duration of a block, potentially leading to a profound block accompanied by hypotension, bradycardia, and in severe cases, cardiac arrest. Reducing the amount of local anesthetic lowers the severity of low blood pressure but affects the effectiveness of anesthesia. Recent studies have shown that intrathecal midazolam enhances the effectiveness of local anesthetics in spinal anesthesia by interacting with the BZD-GABA receptor complex at the level of the spinal cord. This interaction results in localized pain relief without causing any damage to the nerves [9]. Midazolam is classified as a benzodiazepine medication and has shown distinct analgesic properties when used in intrathecal anesthesia. There are benzodiazepine receptors throughout the neurological system, including the spinal cord, which exhibit interactions with gamma-aminobutyric acid (GABA) receptors [10]. Intrathecal administration of Midazolam at dosages ranging from 1 to 2 mg had a beneficial impact on both post-surgical pain and chronic pain management. Animal investigations have shown that intrathecally given midazolam does not have any neurotoxic effects [11]. Sharifi et al. conducted a research demonstrating that the addition of midazolam to bupivacaine decreased the duration of spinal anesthesia. The research demonstrated that the addition of midazolam to bupivacaine resulted in a decrease in the duration of motor block[12]. Additionally, they demonstrated that the inclusion of midazolam with bupivacaine resulted in an extended duration of spinal anesthesia. Imani et al. performed another investigation which revealed that the addition of midazolam to bupivacaine resulted in a considerable reduction in the duration of spinal anesthesia. Furthermore, it was shown that the inclusion of midazolam with bupivacaine resulted in a decrease in the duration of motor block [13]. The current investigation saw comparable results.

Karbasfrushan et al. observed that the concurrent administration of bupivacaine and intrathecal midazolam produced a potent anesthetic agent that effectively alleviated pain. While the sedative onset was quicker, the experimental group had a greater occurrence of nausea and vomiting [14]. The duration of effective pain relief and the time for the reversal of sensory pain relief was same in both groups.The present investigation yielded comparable findings to those of Chavda et al. and Prakash et al., who performed a study to examine the pain-relieving effectiveness of two different dosages of intrathecal midazolam in combination with bupivacaine for spinal anesthesia in patients having cesarean birth. The researchers determined that the addition of 2 mg of intrathecal midazolam to bupivacaine resulted in a modest increase in the duration of pain relief after surgery [15,16]. Ho KM et al. conducted a meta-analysis and found that the addition of intrathecal midazolam to other spinal medicines enhances pain relief during cesarean birth and minimizes the occurrence of nausea and vomiting. Midazolam has antinociceptive properties and enhances the efficacy of local anesthesia when administered by neuraxial block, with little occurrence of notable adverse effects. Administering a tiny, weakened amount of midazolam directly into the spinal canal (1 to 2.5 mg) does not seem to prolong the loss of motor function, increase the likelihood of breathing difficulties, or cause temporary neurological impairments [17]. In a study conducted by Sanwal MK et al., the researchers examined the impact of intrathecal midazolam in reducing the amount of bupivacaine needed for

subarachnoid block during cesarean section. The study indicated that a combination of 7.5 mg bupivacaine with 2 mg midazolam is the most effective dosage ratio for subarachnoid block in cesarean section procedures [18]. By administering 2 mg of intrathecal midazolam, it is feasible to decrease the dosage of bupivacaine from 2.2 mg to 1.5 mg, while still achieving the same level of surgical anesthetic. This adjustment results in a lower occurrence of hypotension and other associated adverse effects. Administering medicines in combination intrathecally leads to a sustained and enhanced analgesic effect compared to administering each agent individually. When many medications are used together, the dosages of the drugs are also decreased, providing an additional benefit in preventing the negative effects that are connected to the dosage.

CONCLUSION

The use of intrathecal midazolam with bupivacaine decreases the time it takes for sensory and motor block to occur, greatly extends the duration of pain relief, and does not lead to an increase in problems among patients having cesarean birth.

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