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Effects of Intrathecal Midazolam (1mg) with Hyperbaric Bupivacaine 0.5% (15mg) for Spinal Anesthesia for Caesarean Section

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ABSTRACT

Background: Intrathecal adjuvants are commonly used to enhance the efficacy of spinal anesthesia, particularly in cesarean sections. Midazolam, a benzodiazepine, has been studied for its potential analgesic and sedative effects when combined with local anesthetics. This study aims to evaluate the effects of intrathecal midazolam (1 mg) in combination with hyperbaric bupivacaine 0.5% (15 mg) for spinal anesthesia in cesarean section patients, assessing its impact on the duration of anesthesia, postoperative analgesia, hemodynamic stability, and adverse effects. **Methods:** A cross-sectional study was conducted at Qazi Hussain Ahmad Medical Complex, Nowshera, following approval from the institutional ethics committee. A total of 60 patients scheduled for elective cesarean section were included, with the sample size calculated using the WHO sample size calculator. Written informed consent was obtained from all participants. The study period spanned from June 2024 to December 2024. Key parameters assessed included the onset and duration of sensory and motor blockade, postoperative pain relief, hemodynamic changes, and the incidence of complications such as nausea, vomiting, hypotension, and sedation. **Results:** The two study group total number of participants 60 each group of 30, variables included age, weight, height and ASA physical status. The sensory block were study with Holleman's scale, group BM sensory block onset time is (93%) more than group B that is (90%). Motor block were study by Bromage's scale and greater in group BM (100%) and less in group B(90%). Midazolam had profound antiemetic effects, as nausea and vomiting were not observed in the group BM and observed in 33% of patients in the group B. The post-operative analgesia time was evaluated by the time of first rescue analgesia requirement. The duration of post-operative analgesia was longer in the group BM (mean=67.93) compared to the group B (mean=28.34). **Conclusion:** Addition of midazolam with bupivacaine for intrathecal block enhanced the efficacy and effectiveness of sensory block and prolonged the post operative analgesia time. Post-operative complications were study in both groups. Intra-op and post-op nausea and vomiting in group BM (3.3%) and (13.3%) in group.

INTRODUCTION

In 1899 the Dr. August bier was carried out his first spinal anesthesia for lower extremity and abdominal surgery and this become standard practice worldwide.(1)

Major disadvantage of single local anesthetic is limited duration of action. A number of adjuvants(ketamine, opioids, neostigmine) are added to intrathecal local anesthetic for prolonged spinal anesthesia and postoperative analgesia.(2) Midazolam produce antinociception and potentiate the effect of local anesthetic in intrathecal spinal anesthesia by different mechanisms such as (GABA-A) receptor in lamina II of the dorsal horn, intrathecal midazolam is involved in the release of an endogenous opioid acting at spinal **δ** receptors without significant side effects(3,4) Intrathecal opioids, clonadine, ketamine and adrenaline in combination with local anesthetics are used but limited in practice due to some adverse effects such as itching ,nausea, urinary retention, sedation, ileus and life threating respiratory depression(5).

Benzodiazepines are drugs which are commonly used for anxiety, sedation and anti convulsion include diazepam, midazolam, and lorazepam, as well as the

selective antagonist flumazenil(6). Midazolam is supplied as hydrochloride salt with a pH less than 4.0 (*buffered to an acidic pH of (3.5*). this is important because midazolam displays pH-dependent solubility. It remains open at pH value of <4, thus maintaining drug´s water solubility.(9) Midazolam exerts its effect by occupying benzodiazepine receptor that modulates γ-amino butyric acid (*GABA*), the major inhibitory neurotransmitter in the brain. Benzodiazepine receptors are found in the olfactory bulb, cerebral cortex, cerebellum, hippocampus, substantia nigra, inferior colliculus, brain stem, and spinal cord. Midazolam, a water soluble benzodiazepine is used via intrathecal route for the treatment of acute perioperative ,chronic and cancer pain.(13) The rationale for the use of intrathecal midazolam focuses on the awareness that it is an agonist at the benzodiazepine binding site, a subunit of the pentameric gammaaminobutyric acid (*GABA-A*) receptor. Agonist occupancy of the benzodiazepine binding site enhances the activity of GABA at the GABA-A receptor. In neurons, this typically serves to decrease excitability. Midazolam intrathecal induced analgesia is spinally mediated binding sites are GABA receptors, mostly present in the dorsal root of nerve cells, with maximum concentration found with lamina II of the dorsal nerve cells, a region that plays role in processing nociceptive and thermoceptive stimulation.(14)

The intrathecal midazolam across species broadly confirms the safety, the analgesic activity of the molecule and its benzodiazepine pharmacology, and the lack of irreversible effects.

Intrathecal midazolam was originally shown to have antinociceptive properties in animals in the early 1980s . Valentine et al. studied the effect of intrthecal midazolam in 1996, along with hyperbaric bupivacaine for caesarean section surgery under spinal anesthesia and found no side effects.(14) Yegin et al. in 2004, conducted a study on the analgesic and sedative effects of intrathecal 2mg preservative free midazolam in perianal surgery under spinal anesthesia . They found that the addition of midazolam with bupivacaine produces a more effective and longer analgesia with a mild sedative effect in patients in the experimental group.(16)

One year later Agrawal et al. investigated postoperative pain relief following intrathecal administration of 1mg preservative free midazolam with bupivacaine in patients scheduled for elective lower abdominal, caesarean section and endoscopic urological surgeries. They showed that intrathecal midazolam and bupivacaine provide longer duration of postoperative analgesia as compared to intrathecal bupivacaine alone, without prolonging time for dermatomal regression. intrathecal midazolam appears to improve perioperative analgesia and reduce nausea and vomiting during caesarean section surgery found by Prakash et al.(17) in 2011, Shadangi et al. concluded that the addition of preservative free midazolam to bupivacaine intrathecally resulted in prolonged postoperative analgesia without increasing motor block.(18) The use of intrathecal midazolam also decreases the incidence of postoperative nausea vomiting (*PONV*). Moreover, intrathecal midazolam does not have any clinically significant effect on perioperative hemodynamics.(19) To evaluate the efficacy of 1mg of intrathecal midazolam with 15mg of hyperbaric bupivacaine for spinal anesthesia to prolong the duration of analgesia compared to using bupivacaine alone in cesarean section patients. To observe the quality of analgesia during surgery and postoperatively in both groups.

MATERIALS AND METHOD

A cross sectional observational study was conducted in Qazi Hussain Ahmad Medical Complex Nowshera with the permission and approval of research ethics committee and heads of departments. The total sample size of 60 patients was calculated based on the prevalence of the effect of intrathecal midazolam for spinal anesthesia using WHO calculator (easymedstat).

Inform consent was taken from all participants who agreed to take part in the study. The study was conducted from June 2024 to December 2024**.** Data were collected through a questionnaire, which included all the required information related to research.

Sampling and Sample Size

This study adopted a convenience sampling method whereby ASA I and ASA II elective obstetric cesarean section patients included in the study, provided verbal and written informed consent was obtained. All patients had an equal chances of being involved in the study. The patients were prepared for the spinal anesthesia, which was performed using the sp 25 and 27 gauge spinal needle. All vital parameters , such is oxygen saturation, pulse rate , blood pressure and ECG were recorded for all patients .Here's the corrected version of your sentence: A total of 60 patients were studied, as calculated using the WHO sample size determination calculator for health studies (WHO, Geneva).

Inclusion criteria**:** Female patients presented for elective cesarean section, all ASA I & II patients, age between 18 to 35 years, contraindication to spinal anesthesia.

And exclusion criteria ,all ASA III & IV class was excluded from the study, patients with documented bleeding disorders i.e. low platelet count, deranged PT/APTT/INR, DIC etc, hypertensive patients, patients with Diabetes mellitus.

Data Collection Procedure

Data collection was done using a standard patient record questionnaire. The following information was recorded on the performa; Patient Age, weight, height, time of spinal block, educational status, type of surgery, preoperative assessment, intraoperative pain,

intraoperative blood pressure, sensory block scale ,motor block scale and sedation scale and postoperative pain duration. Additional complaints such as nausea and vomiting, hypotension, shivering, headache, backache, urinary retention and other neurological complaints were recorded.

The procedure under regional spinal anesthesia was conducted according to the standard protocol of Qazi Hussain Ahmad Medical Hospital as follows: IV access was secured with two cannulas gauge 18. Physiological monitors were attached to the patient and baseline blood pressure, ECG, pulse, SpO^2 were recorded.

Elective cesarean section patients were studied intra operatively after the spinal block performed with bupivacaine 0.5 % with midazolam 1 mg. The sensory block was assessed using Holmen's scale and the motor block was assessed using Bromage's scale in both the group B and group BM. The sedation effect was evaluated using Ramsay's scale in both groups. All patients were observed for intraoperative complications, such as hypotension, nausea & vomiting, pain and respiratory depression and other vital signs, which were documented in the record Performa.

Postoperative data were collected by visiting the post-op units after 12 hours of operation. Patients were asked about postoperative pain onset, duration of analgesia, whether a rescue pain killer was administered or not, postoperative nausea and vomiting(PONV), and other postoperative complications of spinal block.

Data Analysis

SPSS was used for data analysis. Mean and standard deviation are calculated for numerical data and for nominal data frequencies and percentage chi test was applied for the effects and duration of both drugs.

RESULT

The two groups compared with respect to the age, weight, height and American Society of Anesthesiologists physical status. Both group involved similar surgical procedure (caesarean section).The sensory block were study with pinprick stimulus of patient skin at the T10 level with the Holliman's scale, group BM sensory block onset time is (93%) more than group B that is (90%) .

Motor block were study by patient legs movement with Bromage's scale and greater in group BM (100%) and less in group B (90%), Sedation score was study intra operative with Ramsay's scale and sedation was less in group B and more in group BM.

All patients hemodynamic status study with no large difference is observe. It observed that pre-operative hypovolemia have little effect on intraoperative fall in blood pressure.

Midazolam have profound antiemetic effect and nausea and vomiting was(0%) in the group BM and (33%) in group B. Post-operative analgesia time was study by the help of first rescue analgesia requirement, post-operative analgesia duration was more in group BM (67.93%) and (28.34%) in group B.

Addition of midazolam with bupavaicane for intrathecal block enhanced the efficay and effectiveness of sensory block and prolonged the post operative analgesia time.

Post-operative complications were study in both groups. Nausea and vomiting in group BM (3.3%) and (13.3%) in group B .Midazolam decrease the nausea and vomiting in the patients both intraoperative as well as postoperatively.

Post op shivering were present in both group (66.7%) in group BM and (63.3%) in group Patients complaint of headache were (13.3%) in group B and only (6.7%) in group BM. patients complaint of backache were (20%) in group B and (26.7%) in group BM. Urinary retention and other neurological complications were not seen in both groups.

Table 1

Post-operative side effects of group B and group BM patients.

Time(Minutes)	Frequency	Percent	Valid Percent	Cumulative Percent
100	2	6.7	6.7	6.7
105	2	6.7	6.7	13.3
110	1	3.3	3.3	16.7
110	2	6.7	6.7	23.3
120	5	16.7	16.7	40
130	4	13.3	13.3	53.3
135	2	6.7	6.7	60
150	1	3.3	3.3	63.3
160	1	3.3	3.3	66.7
160	1	3.3	3.3	70
165	1	3.3	3.3	73.3
180	1	3.3	3.3	76.7
215	2	6.7	6.7	83.3
60	2	6.7	6.7	90
70	1	3.3	3.3	93.3
90	2	6.7	6.7	100
Total	30	100	100	

Figure 1

Post-operative record of patients

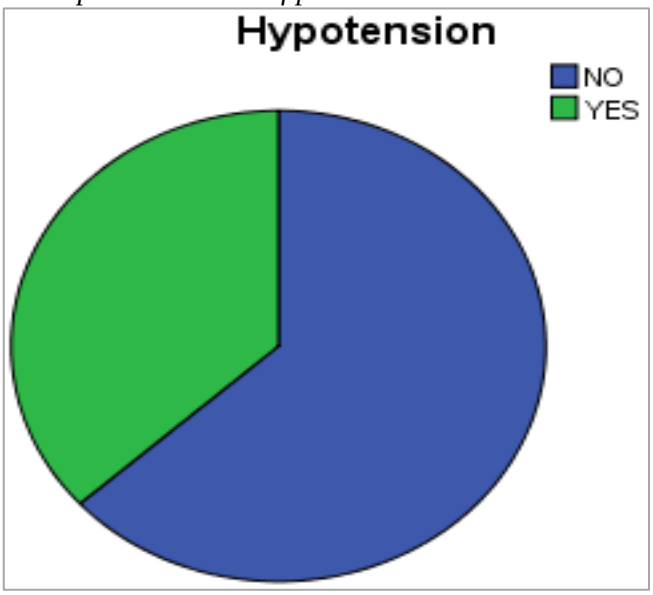

Table 2
Hypotension

	Frequency	Percent	Valid Percent	Cumulative Percent
NO	25	83.3	83.3	83.3
YES	5	16.7	16.7	100
Total	30	100	100	

Table 3
Post-operative analgesia time

Time (Minutes)	Frequency	Percent	Valid Percent	Cumulative Percent
100	2	6.7	6.7	6.7
105	2	6.7	6.7	13.3
110	1	3.3	3.3	16.7
110	2	6.7	6.7	23.3
120	5	16.7	16.7	40
130	4	13.3	13.3	53.3
135	2	6.7	6.7	60
150	1	3.3	3.3	63.3
160	1	3.3	3.3	66.7
160	1	3.3	3.3	70
165	1	3.3	3.3	73.3
180	1	3.3	3.3	76.7
215	2	6.7	6.7	83.3
60	2	6.7	6.7	90
70	1	3.3	3.3	93.3
90	2	6.7	6.7	100
Total	30	100	100	

Figure 2
Group BM

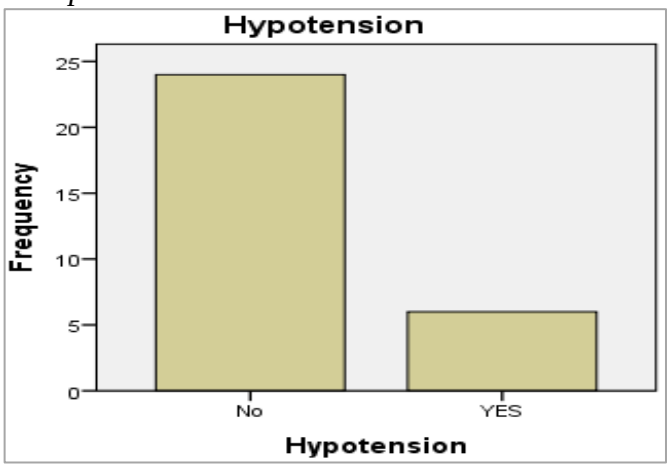

Table 4
Hypotnsion

Hypotension	Frequency	Percent	Valid Percent	Cumulative Percent
NO	23	76.7	76.7	76.7
YES	7	23.3	23.3	100
Total	30	100	100	

Post-operative record of group BM
Table 5

Time (Minutes)	Frequency	Percent	Valid Percent	Cumulative Percent
120	5	16.7	16.7	16.7
135	1	3.3	3.3	20
155	1	3.3	3.3	23.3
170	1	3.3	3.3	26.7
180	1	3.3	3.3	30
190	1	3.3	3.3	33.3
210	4	13.3	13.3	46.7
275	1	3.3	3.3	50
285	1	3.3	3.3	53.3
300	2	6.7	6.7	60
315	2	6.7	6.7	66.7
360	2	6.7	6.7	73.3
420	1	3.3	3.3	76.7
450	1	3.3	3.3	80
480	2	6.7	6.7	86.7
510	1	3.3	3.3	90
600	2	6.7	6.7	96.7
90	1	3.3	3.3	100
Total	30	100	100	

DISCUSSION

Addition of intrathecal midazolam with bupivacaine is widely use an analgesic supplement to combat post-operative pain. The midazolam acts via the spinally mediated benzodiazepines receptors to block antinociception. Prakash et al. (2014) found that the combination of 1 mg intrathecal midazolam with bupivacaine resulted in a mean duration of postoperative analgesia of 6.1 ± 1.0 hours, compared to 3.8 ± 0.5 hours in the bupivacaine-only group In this study ,the addition of midazolam 1mg with bupivacaine spinal (15mg) potentiate the effect of hyperbaric local anesthetic and thus prolong the analgesic effect time up to 4 hours in caesarean section surgery.

In a cohort study, Tucker et al evaluated 574 patients who received intrathecal midazolam and observed the patients for one month for a wide range of symptoms related to neurotoxicity. They concluded that the administration of 2 mg intrathecal midazolam did not increase the occurrence of neurological symptoms.

In this study 30 patients who received intrathecal midazolam and followed after one month for a wide range of symptoms related to neurotoxicity. There were no neurological complaint by patients who received 1 mg midazolam.

In addition to prolonging analgesia, midazolam also increased the duration of both sensory and motor block. The sensory block, assessed by 2-segment regression, was longer in the midazolam group, consistent with findings from study carried by Zhao, W., Lu, X., & Liu, H. (2018).The duration of sensory block was long in midazolam group as assessed by 2-segment regression, which was comparable to the result of previous study.

In this study, that motor block is prolonged in midazolam group as compare to bupivacaine group.

In our study, time to block regression was longer in the midazolam group (360 ± 30 min) compared to the bupivacaine group (126 ± 20 min).

In this study we observed increased sedation level in the midazolam group, consistent with the sedative effects of benzodiazepines. Additionally, midazolam was associated with a reduction in the incidence of

postoperative nausea and vomiting (PONV), a common side effect of spinal anesthesia. This is a particularly valuable benefit, as reducing PONV can improve the patient's overall comfort and reduce the need for antiemetic medications, facilitating a smoother recovery process

CONCLUSION

Combination of benzodiazepines midazolam with local anesthetic bupivacaine for spinal anesthesia better outcomes with compared to bupivaciane alone .the addition of midazolam enhance the effectiveness of block and prolongs the duration of postoperative analgesia.

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