# A COMPARATIVE STUDY OF THE EFFECTS OF INTRATHECAL MIDAZOLAM AND FENTANYL AS ADDITIVES TO INTRATHECAL HYPERBARIC BUPIVACAINE (0.5%) FOR LOWER ABDOMINAL SURGERIES

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**ABSTRACT**

**BACKGROUND**

This prospective randomized double-blind study was designed to compare the analgesic efficacy and safety of intrathecal midazolam and fentanyl as an additive agent to bupivacaine for lower abdominal elective surgeries.

**METHODS**

Sixty patients classified in American Society of Anesthesiologists (ASA) classes I and II scheduled for lower abdominal surgeries were studied. Patients were randomly divided to receive either 12.5 mg hyperbaric bupivacaine plus 1mg midazolam (group BM, n=30) or 12.5 mg hyperbaric bupivacaine plus 25 µg fentanyl (group BF, n=30) intrathecal.

**RESULTS**

The time of onset and the duration of motor blockade were comparable among the groups while the time to sensory block regression was same in group BM and group BF. The duration of postoperative analgesia was similar in group BM and group BF. While it was same for group BM and BF. Symptoms of pruritus and vomiting was more in group BF.

**CONCLUSION**

We conclude that midazolam is as effective as fentanyl in prolonging the durations of both sensory block and analgesia with less side effects.

**KEYWORDS**

Bupivacaine, Midazolam, Fentanyl, Spinal Anaesthesia, Lower Abdominal Surgeries.

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**INTRODUCTION:** Spinal anaesthesia is the most commonly used technique for lower abdominal surgeries as it is cost effective and easy to administer. However, postoperative pain control is a major problem because spinal anaesthesia using only local anaesthetics is associated with relatively short duration of action, and thus early rescue analgesic is needed in the postoperative period. Many adjuvants, such as clonidine, midazolam, fentanyl, and others have been studied to prolong the effect of spinal anesthesia.[1]

The common problem during lower abdominal surgeries under spinal anaesthesia is visceral pain, nausea, and vomiting.[2] The addition of fentanyl to hyperbaric bupivacaine improves the quality of intraoperative and early postoperative subarachnoid block.[3] The addition of opioids to local anaesthetic solution have disadvantages, like pruritus and respiratory depression.

Midazolam produces a synergistic effect on postoperative analgesia when it is administered intrathecally with bupivacaine.[4-7] Earlier reports have shown that administration of intrathecal midazolam with local anaesthetics prolongs the duration of spinal anaesthesia and produces longer postoperative analgesia after lower abdominal and perianal surgeries.[8-12] Not any of these studies report any serious adverse effects in patients receiving intrathecal midazolam. A large cohort study investigating the adverse neurological effects of intrathecal midazolam has also found that there is no association between intrathecal midazolam and neurologic symptoms.[13] However, there are no studies till date that compared the efficacy of intrathecal midazolam with fentanyl in lower abdominal surgeries. Therefore, this prospective randomised double-blind study was planned to compare the analgesic efficacy and safety of intrathecal

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midazolam with fentanyl as an adjunct to bupivacaine for spinal anaesthesia in patients undergoing lower abdominal surgeries.

**MATERIAL AND METHODS:** The study was conducted after obtaining approval from the ethical committee of the institution. Written informed consent was obtained from all patients. The criteria for inclusion were American Society of Anaesthesiologists (ASA) physical status I or II, either sex, age 18–50 years, presenting for lower abdominal surgeries and that for exclusion were patient allergic to drug, heart block/dysrhythmia, or patients on therapy with adrenergic receptor antagonist, calcium channel blocker, and/or ACE inhibitor.

The patients were given 0.5 mg alprazolam orally on the night before surgery. On arrival in the operation theatre, a normal saline infusion at 15 ml/kg/hr was started. A three-lead electrocardiography, non-invasive blood pressure and pulseoximetry was instituted for standard monitoring. Spinal anaesthesia was performed at L3–4 intervertebral space with a 25-G Quincke needle with patients in sitting position. After a free flow of cerebrospinal fluid was obtained, the study drug was injected at the rate of approximately 0.2 ml per second. Sensory blockade assessment was performed by pin-prick sensation at every 2 min till maximum level was achieved, and every 15 min interval postoperatively until regression of block to S2 segment. The motor blockade was assessed at the same time interval using a modified Bromage scale (0=no paralysis, 1=unable to raise extended leg, 2=unable to flex knee, 3=unable to flex ankle). The time of onset and duration of sensory and motor blockade were recorded. The patients received oxygen at 4 lts./min using a face mask during surgery. Intravenous fluids (crystalloids, colloids or blood) were administered for maintenance and according to the surgical blood loss. Heart rate, blood pressure and oxygen saturation (SpO2) were recorded once at baseline, once after intrathecal injection and then every 5 min until the end of surgical procedure. Hypotension (mean arterial pressure <25% of baseline) and bradycardia (heart rate <40 beats/min) were treated with Intravenous mephentermine 6mg and atropine 0.6mg respectively. The surgeon, patient, and the observing anaesthesiologist were blinded to the patient group. Data regarding the highest dermatome level of sensory blockade, the time to reach this level from the time of injection, time to S1 level sensory regression, time to urination, and incidence of side effects were recorded.

During the Postoperative period, the pain score was recorded by using visual analog pain scale (VAS) between 0 and 10 (0=no pain, 10=most severe pain), initially every 1 h for 2 h, then every 2 h for the next 8 h and then after every 4h till 24h. Diclofenac was given intramuscularly as rescue analgesia if VAS was >4. A follow-up was carried out 1 week postoperatively by the blinded anaesthesiologist, who asked about headache as well as postoperative pain and dysesthesia in the buttock, thighs, or lower limbs postoperatively.

Statistical analysis was done using the Statistical Package for Social Science (SPSS 15.0 Evaluation version). For the calculation of the sample size, a power analysis of $\alpha=0.05$ and $\alpha=0.90$, showed that 30 patients per study group were needed. Data are expressed as either mean or standard deviation or as numbers and percentages.[14] Continuous covariates were compared using analysis of variance (ANOVA). The comparison was studied using the Chi-square test or Fisher's exact test as appropriate, with the P value reported at the 95% confidence interval. Value of $P<0.05$ was considered statistically significant.

**RESULTS:** Characteristics of the patients and the duration of surgery were similar in both the groups. There was no significant difference among them respect to the type and duration of surgery (Table A). The time of onset of sensory and motor blockade were also comparable. The regression of sensory blockade to S2 segment was similar. The duration of postoperative analgesia was also same, there was no statistical difference between the fentanyl and midazolam groups (Table B). There was not any significant difference in heart rate and blood pressure among groups. No events of hypotension or bradycardia was recorded. Although the patients who were given intrathecal midazolam were sleepy during intraoperative period, they were easily arousable. No episode of hypoxia or respiratory depression was recorded. Among all the patients of fentanyl group, five experienced postoperative vomiting, while only one in the midazolam group experienced this complication. The difference was not statistically significant. Six patients (30%) complained of pruritus in the fentanyl group while no one in other ($p<0.01$). Two of these patients developed severe pruritus and required diphenhydramine. None of the patients complained of postural headache or any neurological deficit.

| | **Group BM(n=30)** | **Group BF(n=30)** |
|---|---|---|
| Age(yr) | 50.8±13.1 | 53.9±12.8 |
| Weight(kg) | 63.6±9.5 | 62.1±4.1 |
| Gender(m:f) | 17:13 | 18:12 |
| ASA grade I:II | 21:9 | 22:8 |
| Duration of surgery (min) | 53.4±13.1 | 76.4±21 |
| Hysterectomy | 15 | 14 |
| Inguinal hernia | 5 | 6 |
| Urology | 10 | 10 |

***Table A: Demographic and surgical duration data***

**Notes:** Data presented as mean ± SD or number of patients, Group BM: bupivacaine plus midazolam, Group BF: bupivacaine plus fentanyl, ASA: American society of anaesthesiologists.

| | Group BM(n=30) | Group BF(n=30) |
|---|---|---|
| Onset Sensory (min) | 6.8±0.8 | 7.6±0.5 |
| Onset Motor (min) | 7.73±0.6 | 8.33±0.7 |
| Duration Sensory (min) | 217.4±15.7 | 198.8±16.5 |
| Duration Motor (min) | 139.9±12.8 | 145.4±10.9 |
| Duration of Analgesia (min) | 284.2±18.2 | 272.4±15.6 |

***Table B: Block and post-op analgesia***

**DISCUSSION:** This study had demonstrated increase in duration of sensory blockade and postoperative analgesia after subarachnoid injection of midazolam or fentanyl to hyperbaric 0.5% bupivacaine in patients undergoing lower abdominal surgery. The effect of analgesia with intrathecal midazolam was comparable to intrathecal fentanyl, with lesser incidence of pruritus in midazolam group.

Earlier studies demonstrated dose dependent effect of intrathecal midazolam on postoperative analgesia. Kim et al.[8] observed that the addition of 1 or 2 mg of midazolam to intrathecal.

Bupivacaine provided analgesia for approximately 2h and 4h 30min, respectively. In another study Prakash et al.[7] demonstrated that 2mg of intrathecal midazolam, if used as an adjunct to.

Bupivacaine for patients undergoing caesarean section, could provide some degree of prolongation in postoperative analgesia along with decreasing the incidence of postoperative nausea and vomiting. Others also observed that intrathecal midazolam produces significant postoperative pain relief in patients undergoing lower abdominal and perineal surgeries.[9,10,11] Yegin et al.[11] reported that addition of 25µg fentanyl to 18mg hyperbaric ropivacaine for spinal anaesthesia in patients undergoing transurethral resection of the prostate provided postoperative analgesia for approximately 3h 30min; 4 out of 15 patients in fentanyl group experienced pruritus. Though, analgesic efficacy of intrathecal fentanyl had not been compared with intrathecal midazolam in normal patients, a recent study demonstrated that addition of 1 mg intrathecal midazolam to bupivacaine produces much longer duration of anaesthesia (140 min) as compared with 25 µg intrathecal fentanyl (107 min) in opium abusers undergoing lower limb orthopaedic surgery. Another study, comparing intrathecal midazolam with clonidine, reported that 2 mg intrathecal midazolam provided superior analgesia than 30 µgs clonidine with fewer adverse effects in patients undergoing lower abdominal surgeries.[15]

In the present study intrathecal midazolam did not affect the duration of motor blockade. Although a few studies have reported prolongation of motor blockade after intrathecal midazolam, [8,9] a meta-analysis aiming to evaluate the effectiveness and side-effects of intrathecal midazolam in the perioperative setting reported that intrathecal midazolam did not affect the duration of motor blockade.[16] the incidence of pruritus was significantly low in midazolam group compared to fentanyl group.

**CONCLUSION:** In conclusion, the addition of midazolam to intrathecal bupivacaine provides similar potentiation of analgesia as intrathecal fentanyl and appears safe in patients undergoing lower abdominal surgeries. Therefore, intrathecal midazolam can be used as an additive to local anaesthetics with less adverse effects than fentanyl.

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