Original Article

# A Randomized, Double Blinded, Comparative Study between Bupivacaine And Midazolam Combination with Bupivacaine Alone in Spinal Blockage to Evaluate Post Operative Analgesia in cases of Vaginal Hysterectomy

**Chetna Jadeja[1], Purvesh Kacha[2], Khyati Vaghela[3], Vrinda Oza[3], Deepa Gondaliya[1], VA Chhaya[4]**

[1]Associate Professor, Department of Anesthesiology, PDU Medical College, Rajkot, Gujarat, India, [2]Private Practice, Gujarat, India, [3]Assistant Professor, Department of Anesthesiology, PDU Medical College, Rajkot, Gujarat, India, [4]Professor and Head, Department of Anesthesiology, GMRES Medical College, Sola, Ahmedabad, India

## ABSTRACT

**Introduction:** Discovery of benzodiazepine receptors in spinal cord triggered the use of intrathecal midazolam for analgesia. Hence, we compared bupivacaine and midazolam combination with bupivacaine alone in the spinal blockade for post-operative analgesia inpatient posted for vaginal hysterectomy. Aims of our study were to evaluate the duration of sensory blockage, motor blockade, postoperative analgesia and to observe the change in hemodynamic profile and adverse reaction of intrathecal midazolam in cases of vaginal hysterectomy.

**Methods:** A prospective, double-blind, randomized study was carried out in 60 patients, aged 18-60 year, American Society of Anesthesiologist Physical Status I-II in patient posted for vaginal hysterectomy under spinal blockade. The patients were randomly allocated into two groups of 30 patients each. Group BM received bupivacaine (0.5%) 3 ml plus midazolam (1 mg) 0.2 ml and in Group B received bupivacaine (0.5%) 3 ml plus 0.2 ml normal saline intrathecally. Patients were observed for onset and duration of the sensory block, motor block, and analgesia, hemodynamic profile and complication if any.

**Results:** The onset of sensory block, motor block, and anesthesia were comparable in both groups ($P > 0.05$). The duration of sensory block (Group BM - 179.2 ± 35.1 min, Group B -159.9 ± 25.6 min, highly significant) motor block (Group BM - 143.1 ± 35.36 min, Group B -123.4 ± 21.5 min, highly significant) and postoperative analgesia (Group BM - 340.6 ± 88.52 min, Group B - 206.4 ± 62.34 min, highly significant) was significantly prolonged in Group BM compare to Group B. Hemodynamics stability was maintained and no significant side effects were present in both the groups.

**Conclusion:** We conclude that intrathecal midazolam 1 mg is added as adjuvant to 0.5% hyperbaric bupivacaine for longer duration and better quality of postoperative analgesia without prolonging the duration of motor block, in patients posted for vaginal hysterectomy without any adverse effects.

**Keywords:** Bupivacaine, Midazolam, Postoperative analgesia, Spinal blockage, Vaginal hysterectomy

**Corresponding Author:** Dr. Chetna Jadeja, 31, Street No. 2, University Karmachari Society, University Road, Behind FSL, Rajkot - 360 005, Gujarat, India. Phone: +91-9974968442, +91 2812578222. E-mail: chetnagohil@yahoo.com

## INTRODUCTION

Pain is a sensory-physical and emotional experience, it is always the thing to worry for both patient and clinician. Postoperative pain relief is an unresolved issue. Due to pain, postsurgical patients are often unable to breathe adequately, cough effectively, move enough to their own daily needs or participate in their own rehabilitation. This often results in feelings of helplessness; fear, anxiety and depression.[1] Postoperative pain relief helps

in early patient mobilization, reduction of respiratory complications, good patient's outcome, reduced morbidity and patient satisfaction.

There are various methods are used by anesthesiologists to relieve postoperative pain such as postoperative oral opioids, parenteral drugs, local infiltration of drug, intrathecal or extradural drug administration. Regional analgesia has fewer side effects compare to systemic analgesia. One of the methods of providing effective postoperative analgesia is by prolonging the duration of intrathecal bupivacaine by additives such as opioids,[2] clonidine,[3] ketamine,[4] midazolam[5] etc. However, each drug has its own limitations and a need for alternative methods.

Discovery of benzodiazepine receptors in spinal cord[6] triggered the use of intrathecal midazolam for analgesia. Midazolam is known to produce antinociception and potentiate the effect of local anesthetic when given in neuraxial block without having significant side effects.

Midazolam is a short-acting, potent, water-soluble benzodiazepine. It has been used for potentiating the analgesic effect of local anesthetic-induced neuraxial blockade. Spinal analgesia effect of midazolam is mediated by benzodiazepine - gamma-aminobutyric acid (GABA) receptor complex which is abundantly present in the dorsal horn of spinal cord with high density found in lamina II of dorsal horn ganglia. Midazolam also acts on kappa or delta opioid receptors which are also present in substantia gelatinosa of the spinal cord.

Modern anesthesiologists are not concerned only about preoperative and intraoperative care of the patients, but also the postoperative welfare of the patients, the important constituent of which is postoperative analgesia.

Hence, we planned this study to further assess midazolam in spinal blockage for prolong postoperative analgesia and we conduct prospective, randomized, double blinded, comparatives study of intrathecal midazolam – bupivacaine combination with bupivacaine alone in spinal blockage for postoperative analgesia in cases of vaginal hysterectomy.

Aims and objective of our study were to evaluate and compare the duration of sensory blockage, motor blockade and postoperative analgesia, to observe the hemodynamics (heart rate, arterial blood pressure), effects on respiration (respiratory rate, $SPO_2$), complications and adverse events in intrathecal midazolam plus bupivacaine group with bupivacaine group.

## METHODS

After approval from the Institutional Ethics Committee and inform written consent, this study was carried out in our institute (Pandit Dinadayal Hospital, Rajkot, Gujarat) over period of 2 years, from July 2008 to July 2010. The prospective, randomized, double-blind, parallel group, comparative study was carried out in 60 patients of, aged 18-60 year, American Society of Anesthesiologist Physical Status I-II (ASA I and II) in patient posted for vaginal hysterectomy under spinal blockade. After thorough pre-anesthetic evaluation, routine, and specific investigations, patients having a contraindication to regional anesthesia, opioid dependence, history of drug allergy and abuse and any major systemic illness were excluded from the study.

Each patient was informed in detail regarding nature and purpose of the study and were explained 0-10 point visual analogue scale (VAS) on a sheet of paper where (0) labeled as (no pain) and (10) as (excruciating pain) (Figure 1).

The patients were randomly allocated into two groups by computer generated random number sequence in 30 patients each.

Group BM: Patients received an intrathecal injection of bupivacaine heavy (0.5%) 3.0 ml + Injection of midazolam (1.0 mg) 0.2 ml.

Group B: Received intrathecal injection of bupivacaine heavy (0.5%) 3.0 ml + injection normal saline 0.9% 0.2 ml.

Preoperative adequate fasting hours (6-8 h) were confirmed, and baseline vital parameters (pulse rate, blood pressure, respiratory rate, $SPO_2$, and temperature) were recorded. After securing intravenous (IV) line (18 G canula), preloading done with injection ringer lactate 10-15 ml/kg was initiated. All the patients were premedicated with the injection. ranitidine 1 mg/kg IV, injection ondansetron 0.8 mg/kg IV.

The subarachnoid block was performed at the $L_3$-$L_4$ interspace with 23 G spinal needle in sitting or lateral position under all aseptic and antiseptic precautions. After the clear and free flow of cerebrospinal fluid, drugs were given according to assigned group mentioned above. Patients were placed in supine immediately after intrathecal injection. Time of onset of motor and the sensory block was noted. Following confirmation of sensory block by the loss of sensation to pinprick up to $T_{10}$ level, lithotomy position was given to patient and surgery was started. Motor block was assessed by using modified Bromage score (Table 1).

Sedation was monitored by Ramsay's sedation score, pulse rate, arterial blood pressure, electrocardiogram, and $SPO_2$ were monitored immediately after spinal anesthesia and 5 min for first 20 min, and then at 10 min interval till completion of surgery (Table 2).

Bradycardia was defined as the pulse rate below 60 beats/min and treated with injection atropine 0.6 mg IV hypotension was defined as decrease in systolic blood pressure below 20% from baseline and treated initially with IV fluids and then with vasopressors (injection mephentermine 5 mg IV in incremental dose) if required. No analgesic and sedative was given intraoperatively.

After completion of surgery, patients were shifted to the recovery unit. Pulse rate, blood pressure and level of sensory blockage, motor blockage and Ramsay sedation score measured every 60 min interval for 9 h duration. The severity of pain assessed was assessed by using VAS score and measured postoperatively hourly, and if pain occurs (when VAS score reached ≥5), analgesia was provided by intramuscular injection. Diclofenac 75 mg and duration of pain relief was taken as the time from onset of the subarachnoid block to the time of administration of rescue analgesic. The time to regression of sensory block was noted.

**Table 1: Modified Bromage scale**

| Scale | Motor response | Degree of block |
|---|---|---|
| 0 | Free movement of legs and feet with ability to raise extended legs | None |
| 1 | Inability to raise extended leg and knee flexion is decreased, but full flexion of feet and ankle present | Partial - 33% |
| 2 | Inability to raise legs or flex knee, flexion of ankle and feet present | Partial - 66% |
| 3 | Inability to raise leg, flex knee or ankle or move toes | Complete paralysis |

**Table 2: Ramsay's Sedation scale**

| Score | Level of sedation |
|---|---|
| 0 | Awake and agitated |
| 1 | Awake and comfortable |
| 2 | Asleep but arousable |
| 3 | Asleep with sluggish response to verbal command and touch |
| 4 | No response to verbal command and touch |

**Table 3: Demographic data**

| Demographic data | Group - BM | Group - B |
|---|---|---|
| Total number of patients | 30 | 30 |
| Age (years) | 25-60 | 24-60 |
| Mean age (years) ± SD | 45±10.06 | 46±10.11 |
| Weight (kg) | 29-66 | 40-64 |
| Mean weight (kg) ± SD | 48.4±8.49 | 51.6±5.26 |

SD: Standard deviation

The side effects like nausea, vomiting, sedation, amnesia, urinary retention, hypotension and bradycardia were recorded and treated accordingly.

### Statistical Analysis

The data are presented as mean ± standard deviation. The power of the study was 80%. The data of the two groups were compared by unpaired Student's *t*-test, and $P < 0.05$ was considered significant. The sample size was estimated using sample size calculator software with a 95% confidence interval and $P < 0.05$.

## RESULTS

Demographic data were comparable in both the groups ($P > 0.05$) as shown in Table 3.

Heart rates were comparable in both the groups at almost all the times and the differences were statistically not significant as shown in Figure 2. Thus, the addition of midazolam to bupivacaine did not produce bradycardia.

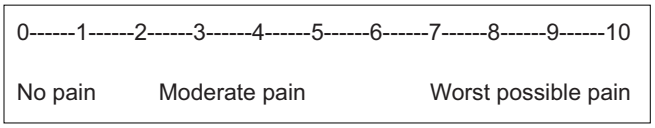


**Figure 1:** Visual analogue scale

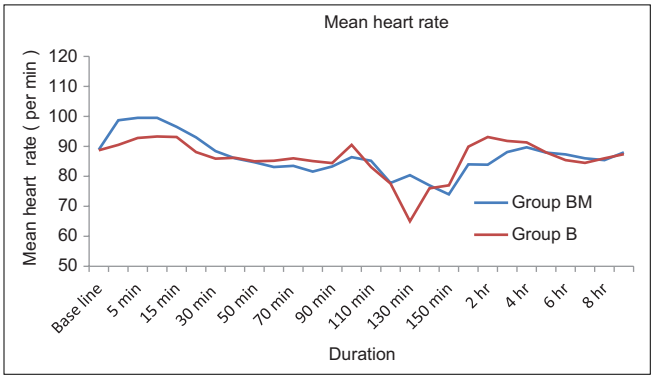


**Figure 2:** Heart rate in both the groups

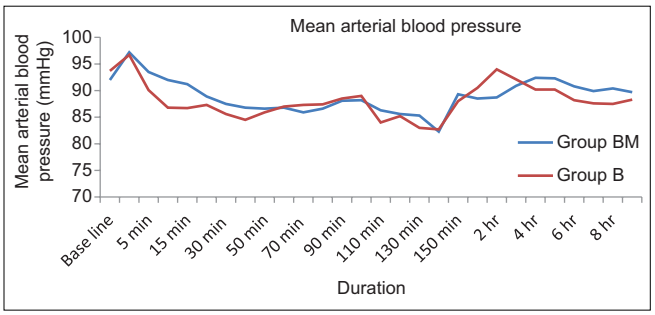


**Figure 3:** Change in mean arterial pressure in both the groups

**Table 4: Onset and duration of motor block, duration of sensory block, duration of surgery, duration of analgesia and Ramsay sedation score**

| Variable | Group BM (mean±SD) | Group B (mean±SD) | *t* value | *P* value | HS/NS* |
|---|---|---|---|---|---|
| Onset of motor block (min) | 5.4±3.36 | 6.4±3.11 | 1.17514 | >0.05 | NS |
| Duration of surgery (min) | 93.5±23.4 | 90.5±20.32 | 0.515256 | >0.05 | NS |
| Duration of sensory block (min) | 179.2±35.1 | 159.9±25.6 | 2.383703 | <0.001 | HS |
| Duration of motor block (min) | 143.1±35.36 | 123.4±21.5 | 2.362827 | 0.001 | HS |
| Ramsay sedation score | 2.4±0.938 | 2.2±1.098 | 0.621 | >0.05 | NS |
| Duration of analgesia (min) | 340.6±88.52 | 206.4±62.34 | 6.676855 | <0.001 | HS |

*HS: Highly significant, NS: Non-significant, SD: Standard deviation

The mean arterial pressure were similar in both the groups, and there were no statistical difference in both the groups as shown in Figure 3, thus, the addition of midazolam did not produce any significant hypotension.

Onset of motor block, Ramsay sedation score, and duration of surgery were similar in both the groups ($P < 0.05$) while duration of motor, sensory and duration of analgesia was prolonged in midazolam group (*P* - highly significant) as shown in Table 4. Thus, the addition of midazolam to bupivacaine prolonged analgesia, as well as motor and sensory blockade.

Duration of sensory block, motor block, and analgesia were higher in Group BM compare to Group M, which were highly significant. Ramsay sedation score and the onset of motor block were comparable in both the groups.

At about 1st h and 2nd h of the postoperative period, mean VAS score is high in Group B, which were statistically significant. At about 3-5 h of the postoperative period, mean VAS score were comparable in both the groups that may be due to rescue analgesic given to both the groups. The mean VAS score after 6th h, up to 9th of the postoperative period were lower in Group BM as compare to Group B as shown in Table 5.

Although the incidence of nausea vomiting was higher in bupivacaine alone group, the difference was not statistically significant. While hypotension was found in more patients (10%) in midazolam group, the difference was statistically not significant as shown in Table 6.

There were no other complications like bradycardia, sedation, amnesia, headache, urinary retention in any group of patients.

**Table 5: Post-operative mean VAS score in the two groups**

| Postoperative time (hours) | Group BM (mean±SD) | Group B (mean±SD) | *t* value | *P* value | Inference |
|---|---|---|---|---|---|
| 1 | 1.333±0.537 | 2.8±1.516 | −4.45 | <0.01 | S |
| 2 | 2.433±0.882 | 4.233±1.764 | −4.42 | <0.01 | S |
| 3 | 3.1±1.009 | 2.533±1.309 | 1.31 | >0.05 | NS |
| 4 | 3.1±1.104 | 2.9±1.247 | 1.37 | >0.05 | NS |
| 5 | 3.03±1.558 | 3.133±0.498 | −1.86 | >0.05 | NS |
| 6 | 2.33±1.558 | 3.4±0.553 | −2.21 | <0.05 | S |
| 7 | 2.33±0.905 | 3.633±0.948 | −2.72 | <0.01 | S |
| 8 | 2.73±0.538 | 3.166±0.859 | −5.32 | <0.01 | S |
| 9 | 2.7±0.932 | 3.766±0.919 | −6.72 | <0.01 | S |

*S: Significant, NS: Non-significant, SD: Standard deviation, VAS: Visual analogue scale

**Table 6: Complication in both groups**

| Complication | Group BM number of patients (%) | Group B number of patients (%) |
|---|---|---|
| Nausea | 1 (3.3) | 2 (6.6) |
| Vomiting | 1 (3.3) | 2 (6.6) |
| Hypotension | 3 (10) | 2 (6.6) |

## DISCUSSION

Postoperative pain relief is an unresolved issue. In the presence of intrathecal midazolam, endogenous opioid neurotransmitters are released to activate delta receptors and decrease nociception receptor activation. This may partially explain the mechanism of benzodiazepine-induced spinal analgesia. In addition, the analgesic effect of intrathecal midazolam may be induced by direct action on benzodiazepine receptors in the spinal cord.[7] It also act via delta receptor[8] and so when given intrathecally they improve analgesic effect of local anesthetics without neurotoxicity,[9] respiratory depression or sedation.[10] Administration of benzodiazepine antagonist like flumazenil has been reported to reverse analgesic effect of intrathecal midazolam, which suggest that anti-nociceptive action are mediated via benzodiazepine GABA-A receptor complex, which are abundantly present in lamina two of dorsal horn ganglia of spinal cord.[11] Intrathecal midazolam has also been found effective in suppressing the reflex response to visceral distension in rabbits[12] and visceral pain in humans in cesarean section.[13] Intrathecal midazolam has been shown to be free of any neurotoxicity or other side effects in doses up to 2 mg and in continuous infusion with doses up to 6 mg/day for long period in man.[14,15]

In the year 1999 Batra *et al*.[16] had done a study in thirty healthy patients scheduled for knee arthroscopy. Patients were divided into two groups. Group B received 2 ml of 0.5% bupivacaine with 8% dextrose, and Group M received 2 ml of 0.5% bupivacaine with 8% dextrose with 2 mg midazolam. None of the patients were sedated with 2 mg intrathecal midazolam, a dose which was twice the dose used in our study (1 mg). In their finding, there was no significant difference in heart rate, blood pressure, respiratory rate, $SPO_2$ and no side effects like nausea, vomiting, itching, urinary retention were present. Our study shows similar findings with comparable hemodynamics profile, respiratory rate, $SPO_2$ ($P > 0.05$) and no significant side effects in both the groups.

In the year 2001, Sen *et al*.[17] studied effects of intrathecal midazolam in cesarean section delivery in a study of 40 women of ASA I and II to evaluate postoperative pain relief with intrathecal midazolam. They also found no significant difference in heart rate, blood pressure, respiratory rate and $SPO_2$, finding similar to our study finding.

In year 2002, Bhattacharya *et al*.[18] did a study to evaluate the duration of analgesia and or pain free period produced by intrathecal midazolam with bupivacaine in patients undergoing major gynecological surgery in a randomized double blinded placebo controlled protocol. Fifty patients undergoing major gynecological surgery (Fothergill and Wardmayo's operation) of ASA I and II were randomly allocated into two equal groups. Group A (n = 25) received 3 ml 0.5% hyperbaric bupivacaine with 0.4 ml of normal saline and Group B (n = 25) received 3 ml of 0.5% hyperbaric bupivacaine with 0.4 ml (2 mg) midazolam. Assessment of pain was done by VAS. A significantly higher VAS was observed in Group A without midazolam as compared to Group B with midazolam ($P < 0.01$), In our study, we also found higher VAS score in Group B in comparison with Group BM ($P < 0.05$).

In 2003, Bharti *et al*.[19] investigated the effect of the addition of midazolam to intrathecal bupivacaine on the duration and quality of spinal blockade. Duration of sensory and motor block was significantly prolonged in their study. Finding which are similar to our finding, duration of sensory block (Group BM - 179.2 ± 35.1 min, Group B - 159.9 ± 25.6 min) and motor block (Group BM - 143.1 ± 35.36 min, Group B - 123.4 ± 21.5 min) which were highly significant in both the groups.

In year 2005, Agrawal *et al*.[5] did a comparative study to see the effect of intrathecal midazolam bupivacaine combination on postoperative analgesia. They found that duration of postoperative analgesia is prolonged without prolongation of sensory block. In our study, postoperative analgesia (Group BM - 340.6 ± 88.52 min, Group B - 206.4 ± 62.34 min, highly significant) was significantly prolonged in Group BM compare to Group B.

Chattopadhyay *et al*. concluded in their review that a small diluted dose (1-2.5mg, <1mg/ml concentration) of preservative-free intrathecal midazolam appears to have few systemic side effects and is free of short-term neurotoxicity.[20]

## CONCLUSION

Hemodynamic data were stable and comparable in both the groups. The onset of sensory and motor blockade were not significant in both groups. Duration of sensory blockade, motor blockade and analgesia were significantly prolonged in midazolam + bupivacaine group compared to bupivacaine alone group.

Hence, we conclude that intrathecal midazolam 1 mg is added as adjuvant to 0.5% hyperbaric Bupivacaine for longer duration and better quality of postoperative analgesia without prolonging the duration of motor block, in patients posted for vaginal hysterectomy without any adverse effects.

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