THE EFFECT OF ADDITION OF INTRATHECAL MIDAZOLAM 1.5 mg TO BUPIVACAINE IN PATIENTS UNDERGOING ABDOMINAL HYSTERECTOMY

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In this prospective, randomized, double blind placebo controlled study, we investigated the postoperative analgesic efficacy of 1.5mg of intrathecal midazolam as an adjunct to bupivacaine for spinal anaesthesia in 100 patients undergoing abdominal hysterectomy. Patients were allocated randomly to 2 groups: Group B received intrathecal 3.5 ml of 0.5% heavy bupivacaine plus 0.3 ml of 0.9% saline; Group BM received 3.5 ml of 0.5% heavy bupivacaine plus 1.5 mg of preservative free midazolam (5 mg/ml). Onset of sensory analgesia, maximum level of sensory block, time to reach it, and time to two segment regression were similar between the two groups ($p > 0.05$). Blood pressure and heart rate were comparable between groups. The mean duration of postoperative analgesia was less in group B compared with group BM. Supplemental analgesic dose requirement with pentazocine was significantly less in Group BM compared with Group B. No neurological deficits were observed. Intraoperative sedation and oxygen desaturation was significantly higher but acceptable in Group BM.

Conclusion:
Intrathecal midazolam 1.5 mg when used as an adjunct to bupivacaine provides better intraoperative sedation and moderate prolongation of postoperative analgesia
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Regional anaesthetic techniques provide an excellent means for managing postoperative pain following gynaecological procedures. Various adjuvants have been added to spinal local anaesthetic to prolong postoperative analgesia. Intrathecal opioids provide effective postoperative analgesia but may be associated with adverse effects such as itching, nausea, urinary retention, sedation, ileus and life-threatening respiratory depression[1]. Other adjuvants such as clonidine, neostigmine and ketamine have also been administered but none have become established in regular clinical use because of their adverse effect profile and their frequent nonavailability in developing countries like India[2,3,4]. Since the early 1980s, intrathecal administration of midazolam has been reported to have antinociceptive action and an effective analgesic agent in animals and humans. In this prospective, randomized, double-blind study, we evaluated the analgesic efficacy of a combination of 1.5 mg of intrathecal midazolam and bupivacaine and compared it with bupivacaine alone in patients undergoing abdominal hysterectomy.

Material and methods:
After approval by the hospital ethics committee and obtaining written informed consent, 100 patients (ASA class I and II), aged 35 to 50 years, scheduled to undergo abdominal hysterctomy were included in this prospective, randomized, double-blind trial. Patients who were not willing for regional anaesthesia or with a known contraindication were excluded. All patients were explained about the eleven point (0-10) Numerical Rating Scale (NRS) of pain assessment. Inj. atropine 0.6 mg IM was the premedication used in all patients. They were randomly divided into two groups of fifty each by a sealed envelope technique. Group B received 3.5 ml of intrathecal heavy bupivacaine with 0.3 ml of normal saline and Group BM a combination of 1.5 mg of intrathecal midazolam (Preservative free Mezolam

of Neon labs) and bupivacaine. This was done using an insulin syringe by a blinded anaesthesia technician. Monitoring of electrocardiography, pulse oximetry and non-invasive blood pressure were done. An 18 gauge intravenous canula was inserted and a preload of 10 ml/ kg of lactated Ringer's solution was administered. Dural puncture was performed at the lumbar 3-4 interspace in the lateral position using a 25G Quincke needle. Time for the onset of analgesia at the dorsum of foot, maximum level of sensory block and the time required to achieve it were noted. Time to regression of analgesia was determined as the time at which the cephalad level of sensory anaesthesia receded two segments. The level of sedation, oxygen saturation, respiratory rate, and blood pressure were recorded every 10 min during the surgery. The intraoperative sedation scores were noted by a blinded observer as follows.

1. Awake and anxious.
2. Awake and comfortable
3. Asleep, responds to oral commands..
4. Asleep, responds to touch.
5. Deeply sedated responding to pain.

This scoring system has been suceesfully used by us in our earlier studies.The level of sedation was assessed every three hours for 12 hours following arrival in the postoperative ward. The regression of spinal level below the incision site was taken as "0" hours. All the patients were shifted to the postoperative ward and the regression was noted by the blinded staff nurse. The postoperative pain scores were studied by the blinded staff nurse as a 0-10 eleven point Numerical Rating scale (NRS). Inj. Pentazocine 30 mg IM was administered when the patient complained of pain or when the NRS exceeded 5. Time to first analgesia (TFA) was noted. When the pentazocine requirements exceeded 30 mg within three hours, Inj. Ketoroloc 30 mg IM was administered as the rescue drug. Pulse, blood pressure, sedation, respiratory rate and other significant postoperative event if any were noted. All data were entered in a proforma, fed into the computer for SPSS and subjected to statistical analysis. Students't test and $\gamma 2$ analysis were performed in appropriate situations and a 'p' value of less than 0.05 was taken as significant.

Results:

The two groups were similar with regard to age ,weight and height. (table 1)

Table 1 showing demographic data.

	Group B	Group BM
Age(years)	43.6±8.6	42.8±7.1
Weight(Kg)	78.4 ± 8.4	74.6±9.3
Height (cm)	148.6± 9.7	149.3±9.5

The level of analgesia was between T6-T8 in all the hundred cases. Onset, duration of anaesthesia were similar in two groups. The surgery was completed within the spinal anaesthetic duration time in all the patients and none needed additional sedatives.(see table 2)

Table 2 showing some features of spinal anaesthesia

	Group B (min.)	Group BM(min.)
Onset	2.5±0.6	2.75±0.56
Time for peak effect	5.75±0.5	6.2±0.6
Duration(anaes)	126.5±13.5	135.5±15.2
Duration(surgery)	70.65±14.5	68.5±12.5

The intraoperative sedation was significantly more in the BM group at twenty minutes after administration of spinal anaesthetic. At all other times, there was no statistically significant difference in sedation level between the two groups. ($p< 0.01$) (table 3).

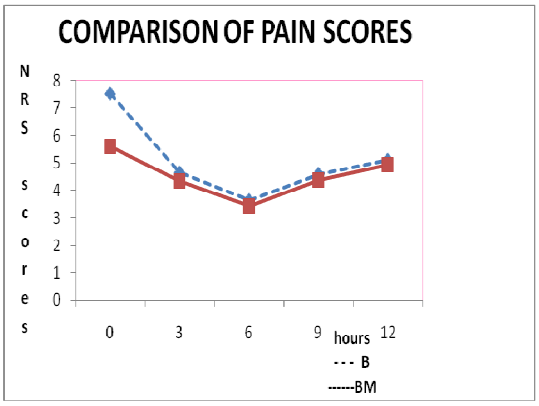
Table 3 Intraoperative sedation scores at twenty minutes.

score	Group B Num. of patients	Group BM Num. of patients
1(↓ sed)	13	3
2	18	8
3	18	15
4	1	**12**
5(↑sed)	0	**12**

Despite adequate anaesthetic level, thirty five patients of group B and only five patients of group BM complained of intraoperative discomfort during abdominal packing. No treatment was

given for the same except oral assurance which settled in around 10 minutes in all the patients.Forty five out of fifty patients desaturated to less than 90 % in the BM group while it was only 3 out of 50 in the plain bupivacaine group. The onset of desaturation was around fifteen minutes after spinal anaesthesia in either group (mean±SD- BM = 16.6±3.8, B=15.8±4.2 minutes) All the desaturated patients were supplemented with 5-6 l/min of oxygen through the Bains circuit for five minutes and stopped. The oxygen supplementation instantaneously improved the saturation to 100 % in all patients. They were watched for further episodes of desaturation in the intraoperative period. All the three patients of Group B were normal while six of forty five patients of Group BM desaturated again after 15 minutes. Similar oxygen supplementation was administered to all these newly desaturated patients. There was no further desaturation in any patient of either group later. All the 100 patients maintained respiratory rate above 12 during the entire study. There was no significant haemodynamic disturbance during the episode of sedation and desaturation. Regarding the pain scores, both the groups were similar except at "0" hours, where the pain was significantly less in Group BM. ($p<0.05$ – fig 1)

Fig 1 showing postoperative pain scores.



The time to first analgesia(TFA) was more in Group BM(31.5±8.2 min) than Group B.(4.2± 1.7 min) There was a significant reduction in the post operative analgesic requirement in Group BM- $p<0.01$-(see table 4.)All the fifty patients of Group B received atleast one dose of rescue analgesic while 27 patients of Group BM received no ketorolac.

Table 4 showing postoperative analgesic requirements.

Analgesic doses.	Group B Num. of patients	Group BM Num. of patients
Pentazocine 30mg	0	5
Pentazocine 60mg	5	23
Pentazocine 90mg	45	22

There was no difference between the two groups with regard to sedation, respiration, nausea, pulse and blood pressure during the postoperative period. There were no neurological complications in any of the cases.

Discussion:

Intrathecal addition of midazolam to local anaesthetics is widely used as an analgesic supplement to combat postoperative pain. The drug probably acts via the spinally mediated benzodiazepene receptors to effect antinociception[5]. All the available studies report effective postoperative analgesia with addition of 1 to 2 mg of midazolam with local anaesthetics[6,7]. In the present study, duration of anaesthesia were similar in the two groups. This is in contrast to that reported by Prakash et al[8] who found that there was a statistically significant decrease in the duration of anaesthesia if midazolam is added. Many other studies have shown the duration of action to be similar[9,10]. Kim & Lee[11] suggested that addition of 1 or 2 mg of intrathecal midazolam prolonged the postoperative analgesic effect of bupivacaine by 2 hr and 4.5 hr, respectively. Valentine et al.[12] have shown that bupivacaine with midazolam showed better analgesia than bupivacaine alone for caesarean section. Batra et al[10] reported an increased duration of postoperative analgesia with intrathecal midazolam 2mg and bupivacaine in 30 patients undergoing knee arthroscopy.Our study confirms the efficacy of midazolam as a postoperative analgesic supplement with significant reduction in analgesic requirements. The duration of block is not changed but there is a moderate prolongation

of early postoperative analgesia. This shows that midazolam prolongs analgesia but not anaesthesia of intrathecal bupivacaine. Some studies[13] show the duration of analgesia to be around 17 hours which was not found in our cases. It is only 31 min when compared to 4 min. with bupivacaine alone. This finding is consistent with the fact that we have not used any preoperative narcotics.Even though, the TFA is only around thirty minutes in the BM group, the persistent antinociceptive effect of intrathecal midazolam was evident in significant reduction in postoperative analgesic and rescue drug requirements in the next twelve hours. There was significant sedation associated with midazolam which starts around 15 minutes after intrathecal administration which also produced significant desaturation. The sedation normalised in around 30 minutes after spinal administration. As this was easily reversible with oxygen supplementation,for its benefits, it is acceptable. The desaturation usually was persistant for 5-10 minutes in many cases.The significant sedation was not observed in earlier studies. There was a good acceptance for visceral noxious stimulus in cases receiving midazolam in our study which goes along with some of the earlier studies[6]. Goodchild et al[14] reported that intrathecal midazolam is not effective against visceral noxious stimulus, but our study does not comply with these findings.The sedation and desaturation was temporary and not observed in the postoperative period. Antiemetic activity of intrathecal midazolam is reported [7] but we did not see a significant difference between the two groups with regard to postoperative nausea and vomiting. A serious risk of intrathecal administration of any drug is its neurotoxicity. Studies in animals and humans[15] have revealed no neurotoxic effects, though two other studies[16,17] observed signs of neurotoxicity. No clinical signs of neurotoxicity in humans have yet been reported. In a cohort study[18] investigating safety in 547 patients, administration of intrathecal midazolam 2mg did not increase the occurrence of neurologic symptoms.We did not encounter any neurological symptoms in the postoperative period. As we have dealt with hysterectomy cases with Foley's catheter in situ,the problem of voiding does not arise.

To conclude, addition of 1.5 mg of intrathecal midazolam to bupivacaine

- Improved intraoperative analgesia.
- Increased intraoperative sedation.
- Produced significant desaturation.
- Effected early postoperative analgesia.
- Decreased postoperative analgesic requirements.

Hence we state, even though the addition of midazolam is advantageous, the risk of intraoperative sedation and desaturation is existent.Its ideal to supplement all patients with oxygen in the intraoperative period. We should be able to manage the side effects and utilize its distinct advantages to improve perioperative outcome.

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