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Original Research Article

Evaluation of intrathecal midazolam (2mg) as an adjuvant to bupivacaine (0.5%) for spinal anaesthesia in orthopaedic surgery: A case control study

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ABSTRACT

Background: Spinal anaesthesia is being routinely used for lower abdominal and lower limb surgeries. Bupivacaine is the commonly used anaesthetic agent because of its longer duration of action. Various intrathecal adjuvants like midazolam are sometimes added to enhance the anaesthetic effects and increase the duration of analgesia. We, hereby evaluated the effects of intrathecal midazolam 2mg as an adjuvant to bupivacaine during spinal anaesthesia in orthopaedic surgery.

Materials and Methods: A total of 60 patients of age 20-50 years were randomly divided into two groups: BM-who received 3.2ml bupivacaine and 0.4ml(2mg) midazolam; and BS-who received 3.2 ml bupivacaine and 0.4ml normal saline.

Results: Mean duration of analgesia was prolonged in the midazolam group (429.33+/-59.54 min) as compared to controls (252+/-42.22 min) (p=0.00). The number of injection diclofenac as rescue analgesic were also significantly less in BM group. Time to achieve maximum sensory level(T4) was also significantly less in BM group. Time to two segment regression and the duration of motor block were more in the midazolam group.

Conclusion: Intrathecal midazolam as an adjuvant significantly prolongs the duration of analgesia and decreases the requirement of rescue analgesia when combined with bupivacaine during spinal anaesthesia. The dose of 2mg seems to safe and effective to achieve the desired results.

1. Introduction

Spinal anaesthesia is used widely for lower limb and lower abdominal surgeries as it has several advantages over general anaesthesia viz. rapid onset, superior blockade, minimal physiological alterations, minimum stress response, cost effectiveness and less chances of postoperative morbidity.[1] Bupivacaine has gained popularity as a spinal anaesthetic agent as it has a long duration of action. It produces adequate pain relief without major side effects at normal doses, however high doses may result in higher levels of sensory and motor blockade as well as may result in arterial hypotension. Moreover, intravascular absorption can lead to seizures, cardiac arrest and even death. Therefore, the need was felt for the use of an adjuvant along with bupivacaine so that the possible side effects due to higher doses could be minimized. Recently, the use of intrathecal adjuvants has become quite popular as they might help in prolonging its duration of anaesthetic as well as analgesic effects.[2] Various neuraxial intrathecal adjuvants which are added to enhance the duration of spinal anaesthesia are opioids, adrenaline, midazolam, dexmedetomidine and clonidine.[3,4] These drugs affect latency of local anaesthetic, duration & quality of analgesia, and reduction of side effects of local anaesthetic drugs.[3]

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Sometimes, these adjuvants can lead to untoward effects such as pruritus, nausea, vomiting, nystagmus, retention of urine, respiratory depression and haemodynamic instability, thence restricting their routine use.[5]

Midazolam, a benzodiazepine analogue is extensively used for its sedative, anxiolytic, and amnesic effects. The use of intrathecal midazolam as an neuraxial spinal analgesic is a somewhat newer concept.[6] It depresses the nociceptive synaptic reflexes by its action on non-opioid GABA-mediated pathways which might have resultant effects in the management of pain.[7] The possible role for GABA in spinal sensory functions is suggested by the relatively high density of GABA receptors, and benzodiazepine receptors in the lamina II of the dorsal horn and moderately high densities in laminae I and III.[8] Intrathecal midazolam in addition exerts its nociceptive effects via the delta-opioid receptors. Its nociceptive effect has been found to be suppressed by the drug naltrindole, a selective delta opioid antagonist.[9] It has been seen that increase in the dose leads to increase in the duration of analgesia with minimal side effects.

There are only few human trials which have evaluated the efficacy of intrathecally administered midazolam-bupivacaine combination. Different doses of midazolam have been used varying from 1mg to 6mg resulting in variability in the duration of post-operative analgesia. Hence, no consensus has been made on the exact dose of midazolam to be used and duration of post-operative analgesia. This study was planned to further assess the intrathecal midazolam-bupivacaine combination and to see the effect of small dose of intrathecal midazolam to enhance post-operative analgesia so as to avoid the possibility of neurotoxicity with higher doses. The present study was conducted by using 2 mg midazolam as an adjuvant to intrathecal bupivacaine to see the effect of post-operative analgesia in Orthopaedic surgery, on prolongation of analgesia, its effect on sensory and motor onset, duration of motor block, time to two segment sensory regression, effect on intra-operative haemodynamic parameters, effect on sedation and requirement of rescue analgesia for 24 hours post-operatively.

2. Materials and Methods

A total of 60 patients of either sex, American Society of Anaesthesiology (ASA) grade I-II, age ranging from 20-50 years (weight 50-80 kg), undergoing lower limb or hip surgeries were included in the study. A valid and informed written consent was taken from the patients prior to the procedure and the study was approved by the institutional ethical committee. Patients were randomly divided into two groups of 30 patients each. Each patient received total 3.6 ml of drug intrathecally: Group 1(BM): 3.2 ml of 0.5% hyperbaric bupivacaine + 0.4ml (2mg) of preservative free midazolam; Group 2 (BS): 3.2 ml of 0.5% hyperbaric bupivacaine + 0.4 ml of normal saline. Both the observers and the patients were blinded to the patient groups and the drugs being administered.

A detailed history about coexisting medical conditions, current medication and previous history of major surgeries was taken. Patients with bleeding or coagulation abnormalities, peripheral neuropathy, raised intracranial pressure, demyelinating central nervous disorders, spinal deformities, local sepsis, psychiatric diseases, valvular heart diseases, previous history of hypersensitivity to amide anaesthetics, and uncooperative or unwilling patients were excluded from the study. Thorough general physical examination was conducted and vital parameters (heart rate, blood pressure, respiratory rate and temperature) were recorded. Laboratory investigations were reviewed including haemoglobin, blood sugar levels, renal function tests and 12 lead electrocardiography. The patients were explained about numerical pain assessment rating scale (0-10; 0 for no pain and 10 for worst pain).

2.1. Procedure

Monitoring of the patients was started with heart rate (HR), non-invasive blood pressure, pulse oximeter and electrocardiogram. Intravenous (I.V.) line was secured with 18-gauge cannula and I.V. infusion was started with ringer lactate. $L_3 - L_4$ interspace was identified in the sitting position and 26 gauge quincke needle was inserted under aseptic conditions. Drug was delivered slowly in the subarachnoid space over 1-2 minutes and patients were kept in supine position without any head tilt. The recording of mean arterial pressure (MAP), HR and peripheral oxygen saturation (SpO_2) was done every 5 minutes intra-operatively.

2.2. Sensory block

The onset of sensory block was measured from the time of injection of the drug into subarachnoid space to the attainment of complete analgesia at the level of T_{10}. Pin prick method (with 23- gauge hypodermic blunt needle) was used to check the level of sensory block achieved bilaterally, with the dermatomal level being tested every 2 minutes till the highest level was stabilized for four consecutive tests. Maximum sensory level achieved was noted and assessment was continued every 10 minutes till there was two segment regression of the block. Duration of sensory block was measured as the time from the onset of the sensory block to the time taken for two segment regression of the block from the maximum sensory block level. During the tracking of sensory block levels following things were noted:

1. The maximum sensory block level attained.
2. Time to achieve this maximum sensory block level.
3. Time to 2 segment regression of the sensory block from the maximum level.

2.3. Motor block

The onset of motor block was assessed every 2 minutes till motor block level 2 or 3 was achieved (according to Modified Bromage Scale).

2.4. Modified bromage scale

1. No motor block
2. Inability to raise extended leg; able to move knees and feet
3. Inability to raise extended leg and move knee; able to move feet
4. Complete block of motor limb

The duration of motor block was taken as the time from complete motor block (Modified Bromage 2 or 3) to time when lower limb can be moved (Modified Bromage 0 or 1).

2.5. Sedation assessment

The degree of sedation was measured with a 4-point scale: 1-no sedation, 2-light sedation, 3-moderate sedation or somnolence, 4-deep sedation.

2.6. Duration of analgesia

Duration of analgesia was measured as the time from the induction of spinal block to the time of administration of rescue analgesia (when pain >5 on numerical rating scale or on patient demand).

2.7. Post-operative pain

Post-operative pain was managed with i.v. injection Diclofenac (aqueous) 75 mg. The total doses used were recorded.

2.8. Side effects

Hypotension (mean B.P. < 65 mm of hg), if any was treated with i.v. fluid bolus and incremental doses of vasopressor agent mephentermine (i.v. 6mg). Nausea, vomiting, shivering or any other side effects were followed up post operatively for 24 hours and treated upon.

3. Observations and Results

The data of the present study was recorded and results were evaluated by using the appropriate statistical tests.

3.1. Demographic data

Both groups were comparable with respect to age, weight, sex distribution and ASA physical status. (Table 1)

Clinical Parameters: (Table 2)

3.2. Sensory assessment

1. Onset of sensory level (at T10): There was no significant difference on statistically comparing the mean time for the onset of sensory level in both the study (BM) as well as the control (BS) groups.
2. Time to achieve maximum sensory level: The mean time taken to attain maximum sensory level was less in patients in BM group as compared to controls. The difference in the two groups was found to be statistically significant (p=0.023).
3. Maximum level of sensory assessment: Nearly half (46.7%) of the patients achieved the maximum sensory T4 level in BM group while only one-third (33.3%) patients could do so in the control group.
4. Time to two segment regression: Patients in the midazolam group took more time to regress to two segment level from the maximum sensory level attained than the patients in the control group. The difference was found to be statistically significant.

3.3. Motor block

1. Onset of motor block: The mean time of onset of motor block was comparable in both the groups. No statistical significant difference was found (p=0.899).
2. Duration of motor block: The mean duration of motor block was found to be more in midazolam group as compared to controls. This observation was statistically significant (p=0.001) suggesting that the midazolam significantly increased the duration of motor block.

3.4. Duration of analgesia

The mean value of duration of analgesia in BM group was 429.33+59.535 minutes whereas the mean value in control group was 252+42.215 minutes. On applying t-test, the values were found to be statistically highly significant (p=0.00). These findings suggest that intrathecal midazolam significantly increases the duration of analgesia.

3.5. Rescue analgesia

Patients of midazolam group had significant prolongation of post-operative analgesia. Their demand of rescue analgesia (number of inj. diclofenac aqueous solution) was also less compared to the control group and the difference was found to be statistically significant.

3.6. Sedation score

Preoperative scores: Patients in both the groups did not had any sedation in the pre-operative period (sedation score-1) and hence were comparable to each other.

Intra-operative sedation score: Intra-operatively sedation score was noted at 30 minutes from the start of surgery.

Table 1: Demographic parameters

N (No. of cases)	Group 1 (n=30)	Group 2 (n=30)	Total 60	
	Mean + SD			p-value
Age (years)	38.27±9.14	36.80±11.30	-	0.583
Weight (kg)	62.6±7.85	62.7±7.79	-	0.974
Sex (M:F)	2:1	2.3:1	-	0.781

Table 2: Clinical parameters

a) Sensory block					
1) Onset(min)		2.27+0.691	2.40+0.770	-	0.483
2) Time to maximum level (min)		9.20+2.265	10.43+1.813	-	0.023
3) Maximum sensory level assessment					
T4	Count	14	10	24	
	% in Group	46.7%	33.3%	40.0%	
T5	count	7	10	17	
	% in Group	23.3%	33.3%	28.3%	
T6	Count	9	8	17	
	% in Group	30.0%	26.7%	28.3%	
T7	Count	0	2	2	
	% in Group	.0%	6.7%	3.3%	
4)Time (min.) to two segment regression		137.67+24.167	113.33+22.180		0.00
b) Duration of Analgesia (min.)		429.33+59.535	252+42.215		0.00
c) Rescue analgesia(No. of Inj. Diclofenac)		1.93±583	3.0±3.0		0.00
d) Motor block (min.)					
1) Onset		3.667+1.061	3.7+0.952		0.899
2) Duration		209.3+23.916	188.7+23.154		0.001
e) Mean sedation scores					
1)Pre-operative		1+0.00	1+0.00		
2)Intra-operative		2.37+0.490	1.33+0.479		0.00
3)Post-operative		1.07+0.012	1+0.00		
f) **Side effects**					
Nausea, shivering, bradycardia, respiratory depression		Nil	Nil	Nil	0.00
Hypotension		13.3%	46.7%		

In midazolam group, 63.3% patients had sedation score 2 and rest 36.7% of patients had sedation score 3. While in control group, 66.7% patients had sedation score 1and 33.33% patients had sedation score 2. On comparing statistically, intra-operative sedation score was found to be statistically highly significant (p=0.000) inferring that midazolam when given intrathecally also causes sedation which may reduce anxiety and increase patient comfort, and reduces requirement of intravenous sedatives.

Post-operative sedation: Post-operatively, only 6.7% patients in midazolam group reported light sedation (sedation score 2). Rest of the patients (93.3% patients in group BM and 100% patients in controls) had no sedation post-operatively. The difference was not found to be statistically significant.

3.7. Haemodynamic parameters

Mean arterial pressure(MAP), Heart rate(HR) and SpO_2 were recorded in both the groups from the start of surgery and readings were taken after every 5 minutes till the completion of the surgery. The mean value of HR and SpO_2 in both the groups were found to be comparable and statistically not significant. The mean of MAP at the start of surgery to first 30 minutes of surgery were not significant and statistically comparable. Patients in the midazolam group had significant fall in mean arterial pressure at 35 and 40 minutes of the surgery (p-0.01, p value 0.03 at 35 & 40 min. respectively). Other values were found to be comparable in both the groups and statistically non-significant.

Table 3: Various relevant past studies assessing the Bupivacaine and midazolam combination in spinal anaesthesia

Title of the study	Dosage of drugs used	Duration of analgesia (minutes)	Rescue analgesia	Time to achieve maximum sensory level	Time to 2 segment regression	Duration of motor block	Sedation scores	Intra-operative haemodynamics	Side effects
Present study*	3.2 ml of bupivacaine (BP) + 2mg midazolam (MZ)	429.33+59.44 min (vs 252 + 42.22 min. in controls)	1.93 + 0.58 injections vs 3.0 + 3.0 injections diclofenac	9.20 + 2.26 min in BM group vs 10.43 + 1.81 min in controls	137.67 + 24.17 min. in BM group vs 113.33 + 22.18 min in controls.	209.3 + 23.92 min in BM group and 188.7 + 23.15 min in controls.	Significant intra-operative sedation noted at 30 minutes	Decrease in MAP at 35 and 40 min. in group BM than controls	Nil, less hypotensi-on in BM group than controls
Abd El Eziz [1]	3.5 ml BP+ 3.0 mg MZ	463.8 + 16.1 min in MZ group vs. 297.1 + 26.5 in controls	1.52 + 0.51 vs 2.45 + 0.31 (Tenoxicam 20-40 mg), 1 vs 4 inj. Pethidine.	8.87 + 1.05 min in study group vs 8.98 + 1.1 min in controls	123 + 14.6 min. vs 122.59 + 15.4 min in controls	Comparable in both the groups	No significant difference in sedation of both groups.	Comparable	Comparable
Shadangi et al [3]	3ml BP+ 2mg MZ	221.1 ± 15.6 min. in study group; vs 121.3 ± 5.4 in controls.	NA	NA	115.8 ± 8.1 min. in study group Vs 90.8 ± 4.1 in controls.	151.8 ± 4.4; study group vs 151.3 ± 3.2; controls.	Sedation score was comparable in both groups.	Comparable in two groups.	Nil
Parthsarthy et al [10]	3.5ml BP +1.5mg MZ	31.5 + 8.2min in MZ group Vs 4.2 + 1.7 in controls.	Less requirement (pentazocine) 90 mg in 22 in study patients vs 45 in controls.	6.2 ± 0.6 in study group vs 5.75 ± 0.5 min in controls.	Comparable in both the groups.	Comparable in both the groups.	Significantly high intra-operative sedation at 20 minutes	Comparable	45/50 patients desaturat-ed to < 90 % in the BM group;only 3/50 in controls.
Gupta et al [11]	3.5ml BP+ 2.5mg MZ	412 ± 57 min midazolam group vs 258 ± 37 min in controls	NA	NA	NA	NA	Comparable	No significant difference in the HR and BP in two groups.	Nil

Continued on next page

Table 3 continued

Joshi et al[12]	3ml BP + (2mg Mz vs 30 ug clonidine)	Midazolam group: 391.64 + 132.98 min vs clonidine group: 296.60+52.77 min)	2.04 + 1.01 vs 2.76 + 0.87 doses of diclo injection	8.64 + 4.05 min in MZ vs 11.44 + 3.87 in clonidine group.	210.84 + 68.4 min in MZ Vs 169.28 + 63.69 in clonidine group.	Comparable in both the groups.	NA	Bradycardia in clonidine group, required vasopressor and atropine	Bradycardia, hypotension more in clonidine group.
Chattopadh-yay et al[13]	2.5 ml BP+ 2mg MZ	320 min in MZ group vs 220 min in controls)	NA	NA	135 minute in MZ group vs 90 min. in controls	255 min. in MZ group vs 195 minutes in controls.	Significant difference in sedation level intra-operative period	Comparable	Nausea, vomiting in patients of midazolam group.
Kim & Lee et al[14]	1ml BP + MZ(1mg vs 2 mg)	2 h: with 1 mg midazolam, 4.5 h: with 2 mg midazolam)	(300 mg paracetamol + 30 mg codeine phosphate) 3.73 control, 2.53 in BM1 and 1.80 in BM2 group	NA	NA	Comparable in both the groups	No sedation in the study as well as control group	Comparable in both the groups	Nil
Yegin et al[15]	2ml BP+ 1mg MZ	199.3+51.1 min. in MZ group vs 167.5+41.5 min. in the control group	Decreased requirement in MZ group.	Comparable in both the groups	Comparable in both the groups	Comparable in both the groups	Scores significantly higher in patients receiving midazolam	No significant difference in the HR, SBP and DBP.	Nil
Punjabi et al[16]	2.5 ml BP+1mg MZ	312.1 min. in the midazolam group and 253.7 min.in the controls.	Decreased requirement in MZ group.	Comparable in both the groups	Comparable in both the groups	comparable in both the groups	Scores comparable in both the groups	Comparable in both the groups	Nil
Bharti et al[17]	3ml BP +1mg MZ	199 min. in study group vs 103 min.	NA	NA	158min. vs 95 min in controls	225 min. in MZ group vs 180 min.	Comparable in both the groups	Comparable in both the groups	Nil

Continued on next page

Table 3 continued

Aggarwal et al[18]	BP+1 mg MZ	17.6+8.87 hours in MZ group vs 4 hours in control group.	Decreased requirement in MZ group.	NA	Comparable in both the groups	Comparable in both the groups	Didn't find any sedation in both groups.	Comparable in both the groups	Nil
Batra et al[19]	NA	All patients in control group received rescue analgesia at a duration of 258+46.8 min. while only one patient in study group		NA	267+67.38 min. in study group vs 229.8+41.4 min. control group	Comparable in both the groups	Comparable in both the groups	Comparable in both the groups.	Nil
Dodawad et al[20]	Group BM: 2 ml BP+ 2mg MZ; Group BC: 2ml BP+0.4 ml distilled water.	357.6 ± 9.74 min in BM vs 201.5± 1.83 min in BC.	1(BM) vs 3(BC) over next 24 hours.	4.1 ± 0.85 min. in midazolam group vs 7.6 ± 1.49 min. in controls	260.6 ± 22.45 min in midazolam group vs170.8 ± 21.17 min. in controls.	190.8 ± 39.74 min. in BM group vs 183.3 ± 20.21 min in controls.	4.64 in BM group vs 4.72 in controls.	Comparable oin two groups	Less nausea, hypotension and shivering in BM group
Kapdi et al[21]	Group A: 2.0 ml BP + 1 mg MZ; Group B: 2.0 ml BP + 0.75 mg inj. nalbuphine	6.5 ± 0.44 hrs (Group A) vs 5.02 ± 0.40 hrs (Group B)	1.5 ± 0.51 (group A) vs 1.7±0.46 (Group B)	3.77 ± 0.50 min in group A vs 3.69 ± 0.49 min in group B	154 ± 4.95 min (group A) vs 125.2 ± 5.44 min (group B)	186.6 ± 5.93 min (group A 173 ± 8.63 min (group B)	Comparable	Comparable	Nausea in 6% and No vomiting in MZ group.

List of abbreviations: BP-Bupivacaine, MZ-Midazolam, NA-data not available, min.-Minutes, hrs-hours.

3.8. Side effects

13.3% patients in group BM and 46.7% patients in group BS had episodes of hypotension. Significant difference was found on statistically comparing the two groups (p=0.005). None of the patients in both the study and control groups had any episode of nausea, bradycardia, shivering or respiratory depression.

4. Discussion

Intrathecal or epidural administration of midazolam leads to dose dependent modulation of spinal nociceptive response in humans.[8] Several researchers have tried to explore the mechanism of analgesic effects of midazolam.[9,22–25] The results of various relevant studies conducted in the past to assess the Bupivacaine-Midazolam combination are being tabulated here. (Table 3)

4.1. Duration of analgesia

The present study showed that there is significant prolongation in duration of analgesia in patients who were administered intrathecal midazolam with bupivacaine than in patients who were given only intrathecal bupivacaine. Similar findings on duration of analgesia were found in various past studies.[1,10] The much more prolonged duration of analgesia in the study by Abd El Aziz1 as compared to our study is probably because of higher doses of the drugs used while study by Gupta et al[11] inferred that 2.5 mg midazolam produces similar prolongation as 2.0 mg midazolam. Intrathecal midazolam was further seen to result in increased prolongation of postoperative analgesia when compared with low dose clonidine (p<0.01).[12] Chattopadhyay et al[13] demonstrated similar findings but showed lesser prolongation in the duration of analgesia compared to our study probably because of use of lesser doses of bupivacaine.Kim et al further demonstrated the dose-dependent analgesic effects of intrathecal midazolam.[14] The prolongation in duration of analgesia was more when 2mg of midazolam was used as compared to 1 mg which itself was more when compared to those receiving only bupivacaine. This study demonstrated lesser increase in the duration of analgesia when compared to our study which can be attributed to the lesser dose of bupivacaine used (1ml) and the different scale used for the assessment of pain. Yegin and colleagues also found longer and more profound analgesia in midazolam group. Post-operative pain scores were found to be significantly lower after first 4 hours in midazolam group (p<.05) as compared to control group.[15] The lesser duration of analgesia in this study when compared to our study might be due to lower doses of drugs used. Punjabi et al also observed similar prolongation of analgesia in the midazolam group (p=0.00).[16] Bharti et al also found significantly longer duration of sensory block in the midazolam-bupivacaine group than the bupivacaine alone group (p< 0.001).[17] The duration of analgesic effects was different from our study as the dose of drugs used were different. The study by Aggarwal et al[18] demonstrated much more prolongation in the duration of post-operative analgesia than our study. It can be explained on the basis that the types of surgery involved in this study were lower abdominal, lower limb, and endoscopic urological surgeries. Patients undergoing endoscopic procedures usually do not perceive much pain hence leading to such a prolongation in the duration of analgesia. Batra et al[19] in their study also observed prolongation in duration of analgesia but differed from our study with regards to the effective duration. This study was done on patients undergoing knee arthroscopy which is not very painful procedure and patients usually perceive less pain post-operatively. Dodawad et al[20] also observed significant prolongation in duration of analgesia in midazolam group (357.6 minutes vs 201.5 minutes) in pregnancy induced hypertensive patients undergoing an elective caesarean section. Kapdi et al[21] on comparing the midazolam and nalbuphine as adjuvants to bupivacaine in partiurents undergoing caesarean section also observed more prolongation in duaration of analgesia with midazolam.

Duration of analgesia in these studies was affected by the dose of intrathecal midazolam used, dose of bupivacaine, types of surgery and type of pain scale used. But all studies found a significant prolongation of analgesia from control group where only bupivacaine was given without additives.

4.2. Requirement of rescue analgesia

Rescue analgesia requirement was significantly decreased in the midazolam group as compared to controls. It was found that difference in the mean value of total inj. diclofenac used was statistically significant (p=0.00). Gupta et al had similar results with regards to requirement of dose of supplemental analgesic drugs.[11] Our study finding was also in concordance with Prakash et al. They found significantly less supplemental analgesic requirements with diclofenac in the midazolam group (p< .001).[26] Kim and Lee have also observed that midazolam-treated groups required less rescue analgesic (oral 300 mg paracetamol+30 mg codeine phosphate) in the first 24 h after surgery (BM2: control-p value <0.01) (BM1: control-p <0.05). These results suggested a dose-dependent analgesic effect of intrathecal midazolam.[14] Parthasarathy et al in their study have also observed significantly less supplemental analgesic requirement in the midazolam group.14 Batra et al found that all patients in control group received rescue analgesia after a mean duration of 258+46.8 minutes whereas only one patient in midazolam group required supplemental analgesia during this period.[19] The requirement of rescue analgesia was also reduced in the study conducted by Dodawad et al (1 vs 3 injections in first 24 hours).[20] Various other studies

have also shown decreased requirement of rescue analgesia in midazolam groups.[1,15,16,18]

4.3. Time to achieve maximum sensory level

Maximum sensory level achieved was T4 in both the midazolam and control groups. Maximum sensory level was achieved in much lesser time in the midazolam group and the difference in the two groups was statistically significant. Other studies found mixed results on this parameter. Joshi et al found that the peak sensory level was achieved in significantly lesser time in the midazolam group (p value <0.05).[12] The present study and other studies which have early onset of peak sensory level may suggest the possible role of intrathecal midazolam in augmenting the fast spread of spinal anaesthesia. Dodawad et al also observed that the maximum sensory level was achieved much earlier in the midazolam group as compared to controls.[20] Other researchers did not find any significant difference in the time to reach maximum sensory level.[10,15,16] It may be due to the reason that the drugs (bupivacaine and midazolam) were used in different dosage and the total volume of drug administered in these studies were different.

4.4. Time to two segment regression

In the present study, there is significant increase in the time to two segment regression of sensory analgesia in the midazolam group as compared to controls. Similar conclusions were made by Batra et al as they also demonstrated that the time to two segment regression of analgesia was longer in study group as compared to control group (p<0.05).[19] Chattopadhyay et al inferred in their study that the two dermatomal segment sensory regression time of sensory block was significantly high with p value 0.00.[13] Punjabi et al inferred that sensory regression time was prolonged significantly in the study group (p=0.00).[16] Others did not find any significant prolongation in time to two segment regression in the midazolam group when compared to controls.[15,18] Midazolam has possible synergistic effect on sensory block as it blocks the nociceptive pathways in the dorsal horn of spinal cord which can explain the increased time to two segment sensory regression.

4.5. Duration of motor block

Intrathecal midazolam significantly increased the motor block duration in this study (p=0.001). Similar results were found by Bharti et al, where the duration of motor block was prolonged in midazolam group than in the control group (p < 0.01).[17] Chattopadhyay et al. observed similar findings with regards to prolongation in the duration of motor block (p<0.05).[13] Shadangi et al. in their study found increase in the duration of motor block in the midazolam group but the results were statistically insignificant (p=0.51).[3] Increase in the duration of motor block found in the present study and similar other studies may be due to intensification of spinal anaesthetic action of bupivacaine. Few studies were not concordant with our study in terms of increase in the duration of motor block.[10,12,15,16] It may be due to the reason that the drugs (bupivacaine and midazolam) were used in different dosage and the total volume of drug administered in these studies were different.

4.6. Sedation score

The present study did not demonstrate any significant difference in the sedation scores in the two groups, both pre-operatively and post operatively. But patients in the study group experienced significant degree of sedation in the intra-operative period (p=0.00). Our results were comparable with the study done by Nishiyama et al, where it was shown that addition of midazolam to a continuous epidural infusion of bupivacaine provides better post-operative analgesia, amnesia and sedation than bupivacaine alone.[27] Yegin et al have also inferred that sedation scores were significantly higher in patients receiving midazolam with bupivacaine than in patients who received only bupivacaine (p<.001).[15] Similar findings were observed in other studies.[10,13,28] But few studies also did not find sedation in the study as well as control group.[1,3,14,16,18]

High sedation in the midazolam group showed that midazolam when given intra-thecally also have sedative effects. This is beneficial as extra sedatives are not required intravenously. The patient is kept free of anxiety which may lead to better patient tolerability of surgical duration leading to better patient outcome.

4.7. Intra-operative haemodynamics

MAP, HR and SPO_2 were assessed intra-operatively in the present study. Mean values of MAP for first 30 minutes of surgery were not significant and statistically comparable. The decrease in the MAP readings at 35 minutes and 40 minutes in midazolam group compared to controls may be explained by the more anxiolytic effect of intrathecal midazolam which manifests mainly after 30 minutes of surgery. Values of heart rate and SPO2 were found to be comparable between the two groups. Various other studies also did not find any significant difference in haemodynamic variables like heart rate, blood pressure.[11,13–16,18–21]

4.8. Side effects

The patients did not have any episodes of intra-operative or post-operative nausea and vomiting in our study. Further, it has been observed that intrathecal midazolam (2 mg) as an adjuvant to bupivacaine significantly lowered the incidence and severity of intraoperative and immediate postoperative nausea and vomiting in partiurents scheduled for elective cesarean section.[29] Patients in the study group

had significantly less episodes of hypotension than those in the control group. This is in concordance with observations by Joshi et al.[12] No such findings were observed in many of the previous studies.[3,10,11,13–16,18] These findings suggest that midazolam does not increase the episodes of hypotension but patients in this group has significantly low incidence of hypotension which implies that midazolam may contribute to hemodynamic stability. More studies need to be done to assess this parameter with more number of patients.

5. Conclusion

Preservative free midazolam at a dose of 2 mg seems to be an effective and safe adjuvant to bupivacaine in spinal anaesthesia as it prolongs the duration of post-operative analgesia and reduces the requirement of rescue analgesia. It is being hoped that this study will help to strengthen our existing knowledge about the use of intra-thecal midazolam in various doses in spinal anaesthesia. In future, long term evaluations of the above modality are required for further elucidation.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare no conflict of interest.

References

1. Aziz ME. Evaluation of intrathecal midazolam as adjuvant to bupivacaine 0.5% for spinal anaesthesia in orthopedic surgery. *Ain Shams J Anesthesiol*. 2009;2:31–4.
2. Berde CB, Strichartz GR. Local Anesthetics. In: Miller RD, Cohen NH, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, editors. Miller's Anesthesia. Philadelphia: Elsevier Saunders; 2014. p. 1038–44.
3. Shadangi BK, Garg R, Pandey R, Das T. Effects of intrathecal midazolam in spinal anaesthesia: A prospective randomised case control study. *Singapore Med J*. 2011;52(6):432–5.
4. Bakshi U, Chatterjee S, Sengupta S, Gupta D. Adjuvant drugs in central neuraxial analgesia-A review. *Internet J Anesthesiol*. 2010;26(1):1–5.
5. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *Anesthesiology*. 1979;51(4):285–7.
6. Khangure N. Adjuvant agents in neuraxial blockade [Serial online]. 2011 Jul 4; ATOTW 230. Available from: http://www.frca.co.uk/Documents/230Neuraxialadjuvants.pdf.
7. Reves JG, Fragen R, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. *Anaesthesiology*. 1985;62(3):310–24.
8. Niv D, Whitwam JG, Loh L. Depression of nociceptive sympathetic reflexes by the intrathecal administration of midazolam. *Br J Anaesth*. 1983;55(6):541–7.
9. Waldvogel HJ, Faull RLM, Jansen KLR, Dragunow M, Richards JG, Mohler H, et al. GABA receptors and benzodiazepine receptors in the human spinal cord: an autoradiographic and immunohistochemical study at the light and electron microscopic levels. *Neuroscience*. 1990;39(2):361–85.
10. Prathasarathy S. The effect of addition of intrathecal midazolam 1.5 mg to bupivacaine in patients undergoing abdominal hysterectomy. *Sri Lankan J Anaesthesiol*. 2011;19(2):81–5.
11. Gupta A, Prakash S, Deshpande S, Kale KS. The effect of intrathecal midazolam 2.5 mg with bupivacaine on postoperative pain relief in patients undergoing orthopaedic surgery. *Internet J Anesthesiol*. 2007;14(2):1–4.
12. Joshi SA, Khadke VV, Subhedar RD, Patil AW, Motghare VM. Comparative evaluation of intrathecal midazolam and low dose clonidine: efficacy, safety and duration of analgesia. A randomized, double blind, prospective clinical trial. *Indian J Pharmacol*. 2012;44(3):357–61.
13. Chattopadhyay A, Maitra S, Sen S, Bhattacharjee S, Layek A, Pal S. A study to compare the analgesic efficacy of intrathecal bupivacaine alone with intrathecal bupivacaine- midazolam combination in patients undergoing elective infraumbilical surgery. *Anesthesiol Res Pract*. 2013;2013:567134. doi:10.1155/2013/567134.
14. Kim MH, Lee YM. Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy. *Br J Anaesth*. 2001;86(1):77–9.
15. Yegin A, Sanli S, Dosemeci L, Kayacan N, Akbas M, Karsli B. The analgesic and sedative effects of intrathecal midazolam in perianal surgery. *Eur J Anaesthesiol*. 2004;21(8):658–62.
16. Punjabi I, Ul-Nisa W, Farooqui A, Ahmed A, Maqbool A. Effects of intrathecal midazolam on quality and duration of spinal anaesthesia with bupivacaine in perineal and lower limb surgery. *Internet J Anaesthesiol*. 2013;32(1):1–11.
17. Bharti N, Madan R, Mohanty PR, Kaul HL. Intrathecal midazolam added to bupivacaine improves the duration and quality of spinal anaesthesia. *Acta Anaesthesiol Scand*. 2003;47(9):1101–5.
18. Agrawal N, Usmani A, Sehgal R, Kumar R, Bhadoria P. Effect of intrathecal midazolam bupivacaine on post-operative analgesia. *Indian J Anaesth*. 2005;49(1):37–9.
19. Batra YK, Jain K, Chari P, Dhillon MS, Shaheen B, Reddy GM. Addition of intrathecal midazolam to bupivacaine produces better post-operative analgesia without prolonging recovery. *Int J Clin Pharmacol Ther*. 1999;37(10):519–23.
20. Dodawad R, Sumalatha G, Pandarpurkar S, Jajee P. Intrathecal Midazolam as an adjuvant in pregnancy induced hypertensive patients undergoing an elective caesarean section: A clinical comparative study. *Anesthesiol Pain Med*. 2016;6(5):1–7.
21. Kapdi M, Desai S. Comparative study of intrathecal preservative-free midazolam versus nalbuphine as an adjuvant to intrathecal bupivacaine (0.5%) in patients undergoing elective lower-segment caesarean section. *Ain-Shams J Anesthesiol*. 2021;13:33. doi:10.1186/s42077-021-00151-9.
22. Goodchild CS, Noble J. The effects of intrathecal midazolam on sympathetic nervous system reflexes in man-a pilot study. *Br J Clin Pharmacol*. 1987;23(3):279–85.
23. Faull RL, Villiger JW. Benzodiazepine receptors in the human spinal cord: a detailed anatomical and pharmacological study. *Neuroscience*. 1986;17(3):791–802.
24. Muller H, Gerlach H, Boldt H. Spasticity treatment with spinal morphine or midazolam: in vitro experiments, animal studies and clinical studies on compatibility and effectiveness. *Anaesthesist*. 1986;35(5):306–16.
25. Goodchild CS, Noble J. The effects of intrathecal midazolam on sympathetic nervous system reflexes in man-a pilot study. *Br J Clin Pharmacol*. 1987;23(3):279–85.
26. Prakash S, Joshi N, Gogia AR, Prakash S, Singh R. Analgesic efficacy of two doses of intrathecal midazolam with bupivacaine in patients undergoing cesarean delivery. *Reg Anesth Pain Med*. 2006;31(3):221–6.
27. Nishiyama T, Matsukawat, Hanaoka K. Continuous epidural administration of midazolam and bupivacaine for postoperative analgesia. *Acta Anaesthesiol Scand*. 1999;43(5):568–72.
28. Shashni S, Nair AS, Gopal T. Clinical effects of intra-thecal midazolam versus intrathecal magnesium sulfate as adjuncts to hyperbaric bupivacaine: A comparative study. *Indian J Pain*. 2013;27:175–81.

29. Singam A, Jaiswal A, Deshpande R, Dhumey T. Intrathecal midazolam for prevention of nausea and vomiting during and after cesarean section under spinal anaesthesia Indian. *J Clin Anaesth*. 2018;5(2):228–32.

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