A STUDY OF INTRATHECAL BUPIVACAINE AND BUPIVACAINE WITH MIDAZOLAM IN LOWER ABDOMINAL SURGERIES

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ABSTRACT

BACKGROUND

Several adjuvants have been tried along with local anaesthetic in spinal anaesthesia for prolonging the duration of analgesia. Intrathecal midazolam produces anti-nociception and potentiates the effect of local anaesthetics. The aim of this study is to study the comparison between intrathecal bupivacaine and bupivacaine with midazolam with spinal anaesthesia.

MATERIALS AND METHODS

This is a comparative, randomised, double-blinded study of 90 patients within the age group of 18 - 60 years with ASA status I or II, undergoing various lower abdominal surgical procedures. They were randomly allocated to one of the two groups, each containing 45 patients as follows: The B group receiving 2 mL of 0.5% hyperbaric bupivacaine (10 mg) and 1 mL of 0.9% saline intrathecally; the BM group receiving 2 mL of 0.5% hyperbaric bupivacaine (10 mg) with 1 mL (1 mg) of preservative-free midazolam. The onset, duration of sensory/ motor block, the time to achieve maximum sensory block and the level of block, time for first rescue analgesia, sedation score, quality of anaesthesia and side effects were noted.

RESULTS

There was no significant difference in the demographic distribution of the patients. There was no statistically significant difference in the onset of the sensory block (p-value > 0.05) and time to achieve maximum level of sensory block in both groups (p-value > 0.05). Mean duration of sensory block or effective analgesia in group BM was 330.88 ± 16.36 minutes, while that in group B was 273.68 ± 15.69 minutes, which was statistically significant (p-value < 0.05). There was no statistically significant difference between both the groups with respect to motor block and quality of anaesthesia. The sedation score was comparable in both groups. The side effect profiles in both groups were also comparable.

CONCLUSION

The addition of 1 mg preservative-free midazolam to 0.5% hyperbaric bupivacaine prolongs the duration of effective analgesia as compared to bupivacaine alone and delays the need for postoperative rescue analgesics without affecting the onset of block and without increasing the risk of side effects.

KEYWORDS

Intrathecal Bupivacaine, Midazolam, Lower Abdominal Surgeries.

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BACKGROUND

Spinal anaesthesia with bupivacaine is routinely administered for lower abdominal surgeries with adequate motor blockage, additionally providing effective pain relief in the initial post-operative period due to its long duration of action.[1] However, the Cardiovascular Collapse/ Central Nervous System (CC/CNS) ratio of bupivacaine is narrow (2.7) with a higher propensity of irreversible cardiovascular collapse.[1]

Therefore, in order to minimise the dose of bupivacaine and to reduce its side effects the use of an adjuvant that would prolong its duration of action and analgesia was required. Intrathecal adjuvants such as ketamine, opioids, clonidine and neostigmine helped in providing faster onset time and prolonged analgesia.[2] Moreover, they diminished the menace of local anaesthetic toxicity, significant hypotension and profound motor blockade. On the other hand, their tendency to cause myriad of side effects such as urinary retention, nausea, vomiting, pruritus and respiratory depression limited their utility.[2] Subsequently, the role of benzodiazepines was explored and it was found that they lead to segmental block of nociception without any adverse effects on the cardiovascular and respiratory systems.[2] Midazolam, a water-soluble benzodiazepine when given by intrathecal or epidural injection exhibits sedative, amnestic, anxiolytic, muscle relaxant, antinociceptive and anticonvulsant properties.[1]

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Aims and Objectives

To study the comparison between intrathecal bupivacaine and bupivacaine with midazolam with spinal anaesthesia.

MATERIALS AND METHODS

This is a comparative, randomised, double-blinded study. Randomisation was done using closed envelope method. The study was initiated after obtaining permission from the Institutional Ethical Committee. It was carried out on 90 patients within the age group of 18 - 60 years with ASA (American Society of Anesthesiologists) status I or II undergoing various lower abdominal surgical procedures under subarachnoid block in Yenepoya Medical College and Hospital, Mangalore, from July 2017 to October 2017. Sample size was taken conveniently. Patients with contraindication for spinal anaesthesia, with known hypersensitivity to the study drugs, with history of drug or alcohol abuse, patients on chronic analgesic or benzodiazepine therapy and pregnant patients were excluded from the study.

Study Period

4 months.

Inclusion Criteria

ASA I and II, Patient's age group: 18 - 60 years, Elective lower abdominal surgeries.

Exclusion Criteria

Patients with contraindication for spinal anaesthesia, Patients with known hypersensitivity to the study drugs, Patients on chronic analgesic or benzodiazepine therapy, Patient with history of drug or alcohol abuse, Pregnancy.

Methodology

Patients were explained about the procedure of spinal anaesthesia and written informed consent was obtained for participation in this study. They were randomly allocated to one of the two groups each containing 45 patients as follows: The B group receiving 2 mL of 0.5% hyperbaric bupivacaine (10 mg) and 1 mL of 0.9% saline intrathecally. The BM group receiving 2 mL of 0.5% hyperbaric bupivacaine (10 mg) with 1 mL (1 mg) of preservative-free midazolam (Inj. midazolam 0.5% ampoule containing 5 mg/ mL diluted to 5 mL with sterile water and 1 mL of this solution was taken). The patients were shown the VAS (Visual Analogue Scale) scoring system and were explained that they would be asked to plot a point on the line that they think will correspond to the degree of their pain at different times. All patients were kept nil per orally for at least 6 hours and pre-medicated with Tab. Alprazolam 0.5 mg on the night before surgery, Inj. Ranitidine 1 mg/kg body weight IV and Inj. Ondansetron 0.1 mg/kg body weight IV at 6 AM on the morning of day of surgery. Pre-loading with 500 mL Ringer's lactate was done before administration of the block.

Procedure of the Block

Venous line was accessed with 18-G cannula and the spinal block was administered in left lateral position in the L_3-L_4 intervertebral space using 25- or 23-G Quincke spinal needle. Under adequate aseptic and antiseptic measures, 2 mL of 0.5% hyperbaric bupivacaine was drawn in a 5 mL syringe and in another 5 mL syringe either 1 mL of preservative-free Inj. Midazolam 0.5% (5 mg/ mL) diluted to 5 mL with sterile water or 5 mL of 0.9% saline was taken and the respective drugs were injected into the subarachnoid space (initially bupivacaine followed by the study drug or 0.9% saline according to random assignment) after obtaining free flow of CSF by an anaesthesiologist who did not participate in the recording of patient's data. The patients were blinded to the drugs given. They were placed in supine position after injection of the drug. Blood pressure (SBP, DBP and MAP), heart rate, respiratory rate and oxygen saturation were monitored intraoperatively at 5 mins interval throughout the duration of surgery, then every hourly till rescue analgesic was administered. Hypotension was defined as fall in systolic BP by more than 20% from the baseline and was managed with IV fluid and Inj. Mephentermine 3 mg in bolus doses. Bradycardia was defined as pulse rate less than 60 per minute and was treated with bolus dose of Inj. atropine 0.6 mg. Respiratory depression was defined as respiratory rate <10 breaths per minute.

The time of onset of sensory blockade (time interval between completion of intrathecal drug injection to the onset of loss of pinprick sensation at T12 level), duration of sensory block or duration of effective analgesia (the time taken from the administration of spinal anaesthesia to the first request of rescue analgesic by the patient), motor blockade (time taken to achieve Bromage motor score= 3, Table 1), duration of motor blockade (time of return to score 0 from Bromage score of 3, Bromage score was assessed at 5, 10, 15, 90, 120, 130 and 140 minutes since administration of intrathecal drugs), level of sedation using Ramsay sedation score (assessed at intervals of 30, 60, 90 minutes after administration of spinal anaesthesia, Table 2), quality of surgical anaesthesia (Table 3), any side effects (nausea, vomiting, urinary retention, sedation, shivering, neurological deficits, post-dural puncture headache and pruritus) were noted. Pain was assessed using Visual Analogue Scale (0-no pain, 10-maximum pain). At VAS score of 4, rescue analgesic in the form of Inj. diclofenac at 1.5 mg/kg was administered and the study was terminated. In case of inadequate spinal blockade, general anaesthesia was given. At the end of surgery, the patients were shifted to the postoperative ward for monitoring of vital signs, appropriate fluid therapy and other treatment.

The raw data of study parameters were entered into Microsoft Excel 2003 spreadsheet and analysed using GraphPad InStat 3 software. The qualitative data were analysed using Fisher's exact test and quantitative data were analysed using two-tailed unpaired student 't' test. A 'p' value < 0.05 was considered to be statistically significant.

RESULTS

The patients participating in the study were between 18 - 60 yrs. of age. The mean age in group BM was 38.45 ± 12.05 yrs. and in group B was 38.38 ± 13.43 yrs. The difference in the age in both the groups was not statistically significant ($p > 0.05$). The group BM consisted of 21 male and 24 female patients, while group B contained 20 male and 25 female patients. The distribution of patients with respect to sex was comparable in both the groups ($p > 0.05$, non-significant). The mean of weight in group BM was 60.88 ± 13.65 kgs, while that in group B was 61.43 ± 12.24 kgs. The difference with respect to weight between both the groups was not

statistically significant. Mean height of the patients in group BM was 157.32 ± 13.84 cm, while in group B the mean was 158 ± 12.38 cm. There was no statistically significant difference in both the groups with respect to height. Group BM consisted of 33 ASA I patients, while in group B there were 31 ASA I patients. No. of ASA II patients in group BM and group B were 12 and 14 respectively. Distribution of patients with respect to ASA physical status carried no statistically significant difference. The patient's characteristics are noted in Table 4.

In group BM mean time required for onset of sensory block was 4.23 ± 0.98 minutes, while in group B the time required was 3.7 ± 1.14 minutes. There was no statistically significant difference in the time required for onset of sensory block. Again, in group BM mean time required for onset of motor block was 6.52 ± 1.19 minutes, while that in group B was 6.39 ± 1.36 minutes. There was no statistically significant difference in the time required for onset of motor block between both the groups. Mean duration of sensory block or effective analgesia in group BM was 330.88 ± 16.36 minutes, while that in group B was 273.68 ± 15.69 minutes. There was statistically significant difference between both the groups with respect to mean duration of sensory block or mean duration of effective analgesia. Mean duration of motor block in group BM was 120.39 ± 4.22 minutes, while that in group B was 121.45 ± 4.02 minutes. There was no statistically significant difference between both the groups with respect to motor block. Time required for onset of the block and duration of block is depicted in Table 5.

On assessing the level of sensory block by pinprick in the group BM 40 patients had sensory block at T12 level, while 5 patients had till L1 level after 5 minutes of administration of spinal anaesthesia. In comparison to this in the group B 41 patients had sensory block till T12, while 4 patients had the same till L1 level. The difference between the two groups with respect to level of block at 5 minutes after administration of spinal administration of spinal anaesthesia was not statistically significant. Again, at 10 minutes after administration of spinal anaesthesia in the group BM 7 patients had sensory block up to T12, 26 patients up to T11 and 12 patients up to T10 level. In the group B 8 patients had sensory block up to T12, 27 patients up to T11 and 10 patients up to T10 level at 10 minutes after spinal anaesthesia. There was no statistically significant difference between the two groups with respect to level of block at 10 minutes after administration of spinal anaesthesia. At 15 minutes of administration of spinal anaesthesia in the group BM 40 patients had sensory block up to T10 and 5 patients had up to T9. In the group B 39 patients had sensory block at T10, while 6 patients had sensory block at T9. There was no statistically significant difference between the two groups with respect to sensory level at 15 minutes after administration of spinal anaesthesia (Table 6).

In the group BM 33 patients were administered rescue analgesia at 4th postoperative hour, 6 patients at 3rd postoperative hour, 4 patients at 5th postoperative hour and 2 patients at 2nd postoperative hour. Similarly, in the group B 42 patients were administered rescue analgesia at 3rd postoperative hour and 3 patients at 2nd postoperative hour. The pulse rate, MAP and respiratory rate were recorded in both groups BM and B at various time intervals during the intraoperative and postoperative period. No statistically significant difference was found in both groups with respect to these haemodynamic parameters.

At 5 minutes after administration of spinal anaesthesia in group BM 34 patients had Bromage score of 2, while 11 patients had score of 3. In the group B 32 patients had Bromage score of 2, while 13 patients had the score 3 at 5 minutes after administration of spinal anaesthesia. This difference was statistically insignificant. At 10 to 15 minutes after administration of spinal anaesthesia, all the patients in both the groups had the score of 3. At 90 minutes after administration of spinal anaesthesia in the group BM, 19 patients had the Bromage score of 2 and 26 patients had the score of 3. In group B 16 patients had the Bromage score of 2, while 29 patients had the score of 3 at the same time. This difference was not statistically significant. At 100 minutes after administration of spinal anaesthesia, all the patients in both the groups had the Bromage score of 2. At 110 minutes after administration of spinal anaesthesia in group BM 35 patients had Bromage score of 1, while 10 patients had the score of 2 compared to 33 and 12 patients in group B who had the same Bromage scores of 1 and 2 respectively at the same time. Again, this difference was not statistically significant. At 120 minutes after administration of spinal anaesthesia in group BM, 24 patients had the score of 0 and 21 patients had the score of 1 compared to 20 and 25 patients belonging to the group B, who had the same Bromage scores of 0 and 1 respectively at the same time. Again, this difference was not statistically significant. At 130 and 140 minutes after administration of spinal anaesthesia, all the patients in both the groups had the Bromage score of 0.

With respect to quality of anaesthesia, there was no statistically significant difference between the groups BM and B (BM: 38-good, 7 fair; B: 36-good, 9-fair). 30 minutes after administration of spinal anaesthesia in the group BM 38 patients had Ramsay sedation score of 2 and 7 patients had the score of 3, while in group B number of patients with similar Ramsay score at the same time were 39 and 6 respectively. 60 minutes after administration of spinal anaesthesia in the group BM 39 patients had the sedation score of 2 and 6 patients had the score 3, while in group B 42 patients had the score of 2 and 3 patients had the score 3. 90 minutes after administration of spinal anaesthesia in group BM 42 patients had the sedation score of 2 and 3 patients had the score of 3, while in group B 41 patients had the score of 2 and 4 patients had the score of 3. Statistically, significant difference with respect to level of sedation was not found between the two groups (p value > 0.05).

In the group BM 31 patients (68.88%) had hypotension following administration of spinal anaesthesia, while in the group B 28 patients (62.22%) had the same. No statistically significant difference was obtained. 4 patients (8.89%) in the group BM and 5 patients (11.11%) in group B had bradycardia. The difference was statistically insignificant. In the group BM 2 patients (4.44%) experienced nausea, while 4 patients (11.11%) in the group B experienced the same. The difference was statistically insignificant. Again 4 patients (8.88%) belonging to the group BM developed PONV (post-operative nausea and vomiting) compared to 7 (15.55%) patients belonging to the group B. The difference was statistically insignificant.

Bromage Score		
Grade	**Criteria**	**Degree of Block**
0	Free movement of legs and feet	Nil (0%)
1	Just able to flex knees with free movement of feet	Partial (33%)
2	Unable to flex knees, but with free movement of feet	Almost Complete (66%)
3	Unable to move legs or feet	Complete (100%)
Table 1		

Ramsay Sedation Score	
Score	**Criteria**
1	Patient is anxious and agitated or restless or both
2	Patient is cooperative, oriented and tranquil
3	Patient responds to commands only
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	Patient exhibits no response
Table 2	

Quality of Surgical Anaesthesia	
Good	No complaints
Fair	Minimal discomfort, relieved by assurance
Inadequate	Patient's complaints of pain, relieved by systemic opioid
Poor	Grossly inadequate block, GA required
Table 3	

Patient Characteristics			
Parameter	**Group BM (mean)**	**Group B (mean)**	**Comment**
Age (yrs.)	38.45±12.05	38.38±13.43	p value>0.05
Sex (M: F)	21:24	20:25	p value>0.05
Wt. (kg)	60.88±13.65	61.43±12.24	p value>0.05
Height (cm)	157.32±13.84	158±12.38	p value>0.05
ASA I	33	31	p value>0.05
ASA II	12	14	p value>0.05
Table 4			

Perioperative Parameters			
Parameter	**Group BM**	**Group B**	**Comment**
Onset of sensory block (min)	4.23±0.98	3.7±1.14	p value>0.05
Onset of motor block (min)	6.52±1.19	6.39±1.36	p value>0.05
Duration of sensory block (min)	330.88±16.36	273.68±15.69	p value>0.05
Duration of motor block (min)	120.39±4.22	121.45±4.02	p value>0.05
Table 5			

Sensory Level of Anaesthesia						
	Group BM			**Group B**		
Level	**5 mins (No. of Patients)**	**10 mins (No. of Patients)**	**15 mins (No. of Patients)**	**5 mins (No. of Patients)**	**10 mins (No. of Patients)**	**15 mins (No. of Patients)**
L1	5	0	0	4	0	0
T12	40	7	0	41	8	0
T11	0	26	0	0	27	0
T10	0	12	40	0	10	39
T9	0	0	5	0	0	6

	Sensory Level at 5 Minutes		**Sensory Level at 10 Minutes**		**Sensory Level at 15 Minutes**	
	Group BM	**Group B**	**Group BM**	**Group B**	**Group BM**	**Group B**
Comments	p value>0.05		p value>0.05		p value>0.05	
Table 6						

Comparison of Bromage Score							
	Group BM (No. of Patients)				**Group B (No. of Patients)**			
	Bromage Score 0	**Bromage Score 1**	**Bromage Score 2**	**Bromage Score 3**	**Bromage Score 0**	**Bromage Score 1**	**Bromage Score 2**	**Bromage Score 3**
5 mins	0	0	34	11	0	0	32	13
10 mins	0	0	0	45	0	0	0	45
15 mins	0	0	0	45	0	0	0	45
90 mins	0	0	19	26	0	0	16	29
100 mins	0	0	45	0	0	0	45	0
110 mins	0	35	10	0	0	33	12	0
120 mins	24	21	0	0	20	25	0	0
130 mins	45	0	0	0	45	0	0	0
140 mins	45	0	0	0	45	0	0	0

	Bromage Score																	
	5 mins		10 mins		15 mins		90 mins		100 mins		110 mins		120 mins		130 mins		140 mins	
	Group BM	Group B	Group BM	Group B	Group BM	Group B	Group BM	Group B	Group BM	Group B	Group BM	Group B	Group BM	Group B	Group BM	Group B	Group BM	Group B
Comment	p value >0.05		~		~		p value >0.05		~		p value>0.05		p value>0.05		~		~	

Table 7

Ramsay Sedation Score during Surgery						
Sedation Score	Group BM			Group B		
	30 mins (No. of Patients)	60 mins (No. of Patients)	90 mins (No. of Patients)	30 mins (No. of Patients)	60 mins (No. of Patients)	90 mins (No. of Patients)
1	0	0	0	0	0	0
2	38	39	42	39	42	41
3	7	6	3	6	3	4
4	0	0	0	0	0	0
5	0	0	0	0	0	0
6	0	0	0	0	0	0

	Sedation Level at 30 mins		Sedation Level at 60 mins		Sedation Level at 90 mins	
	Group BM	Group B	Group BM	Group B	Group BM	Group B
Comment	p value>0.05		p value>0.05		p value>0.05	

Table 8

Side Effects	Group BM	%	Group B	%	Comment
Hypotension	31	68.88	28	62.22	p value>0.05
Bradycardia	4	8.89	5	11.11	p value>0.05
Shivering	2	4.44	4	8.89	p value>0.05
Nausea	2	4.44	4	8.89	p value>0.05
Respiratory depression	0	0	0	0	~
PONV	4	8.89	7	15.55	p value>0.05
Urinary retention	6	13.33	4	8.89	p value>0.05

Table 9

DISCUSSION

Midazolam, the first clinically used water soluble benzodiazepine was manufactured by Walsar and colleagues in 1976. It has been extensively used both in critical care medicine and operating room for its sedative, anxiolytic and amnestic effects; but probable use of intrathecal midazolam as an adjuvant to bupivacaine is a comparatively newer concept in anaesthesia practice.[3] With the discovery of benzodiazepine receptors in spinal cord in 1977, intrathecal use of midazolam for potentiating the effect of anaesthetics used in subarachnoid block was started.[4] It acts through BZD-GABA receptor complex at spinal cord level, specifically GABA-A receptors which are in highest concentration in lamina-II or the dorsal horn ganglia leading to segmental analgesia without any neurotoxic effects. In addition to analgesia, midazolam is helpful for suppressing the reflex response to visceral pain in caesarean sections in humans.[2,5]

In the present study, the demographic characteristics of the patients were comparable. There was no significant difference between the test and control groups with respect to age, sex distribution, weight and height or ASA status.

In this study, the mean time of onset of sensory analgesia up to T12 level was 4.23 ± 0.98 minutes in the test group and 3.7 ± 1.14 minutes in the control group, which was insignificant statistically. This finding was comparable to other studies by Agarwal et al, Punjabi et al, Gupta et al, Vasanthi et al and Kulkarni et al, who reported similar results.[5-9] Also in our study in the group BM mean time required for onset of motor block was 6.52 ± 1.19 minutes, while that in group B was 6.39 ± 1.36 minutes which had no statistical significance. The studies by Vasanthi et al and Punjabi et al also had highlighted the time of onset of motor blockade and it was found that similar to our study (Vasanthi et al- 6.26 mins in control, 6.3 mins in test; Punjabi et al- 9.3 mins in control, 8.2 mins in test). There was no great difference between test and control groups.[5,7]

In the present study, the duration of analgesia in the test and control groups were 330.88 ± 16.36 and 273.68 ± 15.69 minutes respectively. The difference between the two groups with respect to duration of analgesia was statistically significant. This finding is supported by many other similar studies by Nanjegowda et al (duration was increased by 1.5 hrs. in BM group) and Gupta et al (duration was increased by 6.8 hrs. in BM group), who had used this combination for orthopaedic surgeries. The marked increased duration of analgesia in these studies compared to our study (57 minutes) can be attributed to the greater dose of midazolam (2 mg) used by Nanjegowda et al and greater dose of Bupivacaine (3.5 mL) as well as midazolam (2 mg) used by Gupta et al.[8,10] Other studies based on gynaecological procedures by Baduni et al (labour analgesia), Akhtaruzzaman et al (caesarean sections), Karbasfrushan et al (caesarean sections), Parthasarathy et al (abdominal hysterectomies), Sidiq et al (elective gynaecological surgeries) also yielded findings similar to ours.[2,11-14] The duration of analgesia in the test group was increased by 85 minutes in the study by Akhtaruzzaman et al and by 87 minutes in the study by Sidiq et al. The study by Chattopadhyay et al was also done for lower abdominal surgeries like ours, but they used larger dose of anaesthetics (12.5 mg bupivacaine and 2 mg midazolam) and so achieved longer duration of analgesia (100 minutes) in test group compared to our study.[15]

No difference in sedation levels was found in the two groups, similar to studies by Prakash et al and Shadangi et al.[16,17] There was no difference between both the groups with respect to quality of anaesthesia unlike studies by Vasanthi et al and Akhtaruzzaman et al who observed better quality anaesthesia in test group. Also, incidence of side effects viz. hypotension, bradycardia, shivering, nausea, urinary retention and PONV were similar between both the groups in this study comparable to studies by Sidiq et al, Shadangi et al and Vasanthi et al.

CONCLUSION

We conclude that the addition of 1 mg preservative-free midazolam to 0.5% hyperbaric bupivacaine for subarachnoid block in lower abdominal surgery prolongs the duration of effective analgesia as compared to bupivacaine alone and delays the need for postoperative rescue analgesics without affecting the onset of block and without increasing the risk of side effects. It may find a place in regular clinical use as an adjuvant in selective spinal anaesthesia.

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