Original Research Article

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A Comparative Study of Low Doses of Intrathecal Ketamine and Midazolam with Bupivacaine for Infraumbilical Surgeries

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Abstrct

Aim: The aim of this study is to evaluate the effect of the low doses of ketamine and midazolam with bupivacaine intrathecally in terms of duration of analgesia and haemodynamic parameters. *Materials and Methods:* This prospective randomized double blind study conducted in patients posted for Infra umbilical surgeries. Patients with physical status ASA I and ASA II with Infra umbilical surgeries like herniorrhaphy, varicose vein surgery, orthopaedic surgeries with less than 3 hr duration were taken up for the study. *Results:* All demographic details are not significant. With addition of midazolam and ketamine the mean onset of sensory block is quicker compared to other two groups. with addition of midazolam and ketamine the mean onset of motor block is quicker compared to other two groups. With addition of Midazolam and ketamine the maximum sensory level and reached in higher compared to other two groups. With addition of midazolam and ketamine the duration of sensory block and motor block is prolonged compared to other two groups. With addition of ketamine and Midazolam the mean duration of pain free interval is prolonged and rescue analgesics required are less compared to other two groups. In all three groups the mean systolic blood pressure was comparable and they are not statistically significant. The Vasopressors required in Group A and C were compared and they are not statistically significant. In Group B and Group C the sedation score was higher compared to Group A. *Conclusion:* Low doses of preservative free ketamine (0.1mg/kg) and midazolam (0.02mg/kg) when added to bupivacaine intrathecally provides prolonged post operative analgesia without any significant side effects.

Keywords: Intrathecal Ketamine; Midazolam; Bupivacaine; Infraumbilical Surgeries.

Introduction

The term "Spinal Anaesthesia" was coined by Leonard Corning in 1885. In 1898, the first deliberate spinal anaesthesia was given to August Karl Gustav Bier by his assistant Dr. Hildebrandt. The second attempt was done on the theca of Dr. Hildebrandt. Twenty three minutes after the injection of cocaine, Dr. Bier noted "A strong blow with an iron hammer against the tibia was not felt as pain." The simplicity of the technique of spinal anesthesia and its reliability had made it one of the preferred techniques in infraumbilical surgeries.

Bupivacaine when used alone intrathecally produces analgesia for three to four hours, making it unsuitable in cases where the duration of surgery is longer. Different adjuvants such as opioids, clonidine or neostigmine may be added to enhance spinal anesthesia, though their use is limited because of side effects.

Ketamine is a potent analgesic acting as an antagonist at N - Methyl - D aspartic acid receptor sites and has a local anaesthetic action. Intrathecal ketamine has been used as a sole agent or in combination with local anaesthetics. It provides stable haemodynamics but shorter duration of action.

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Midazolam has a spinally mediated anti-nociceptive effect and enhance the analgesic effect of local anaesthetics when used intrathecally. It improves the duration and quality of the spinal anaesthesia, though it does not prevent the haemodynamic instability produced by intrathecal bupivacaine. Hence this study is done to evaluate the effect of small doses of ketamine and midazolam with bupivacaine intrathecally in terms of duration and quality of analgesia and side effect profile.

Materials and Methods

This prospective randomized double blind study conducted in patients posted for Infra umbilical surgeries. Approval from the Ethical Committee was obtained and Written informed consent was taken from all patients

Inclusion Criteria

Patients with physical status ASA I and ASA II with Infra umbilical surgeries like herniorrhaphy, varicose vein surgery, orthopaedic surgeries with less than 3 hr duration were taken up for the study.

Exclusion Criteria

Morbidly obese patients, pregnant women, patient with neurological disease or any contraindication for regional technique were excluded from the study.

Three groups were selected. Patients were randomly assigned to one of the three groups. Patients and anaesthesiologist were blinded to the test drug. The volume of the test drug was kept 3.5 ml in all patients. After attaching the patients to monitors, baseline values of heart rate, systolic, diastolic, mean arterial pressure and oxygen saturation were noted. They were preloaded with 10 ml/kg intravenous crystalloid solution.

Procedure

Under strict aseptic precaution, lumbar puncture was performed at L3-L4 interspace using a 25-G Quincke's needle. After achieving free flow of cerebrospinal fluid the study drug was injected into the subarachnoid space.

Study Groups

Each study group consisted of 30 patients. Patients in all 3 groups received 3 ml of bupivacaine (heavy) 0.5%. In addition, patients in group B received preservative free ketamine 0.1 mg/kg and those in group C received preservative free ketamine 0.1mg/kg and midazolam 0.02 mg/kg intrathecally. The exact amount of ketamine and midazolam were measured using a tuberculin syringe and the final volume of the test drug in all the groups was made up to 3.5 ml by adding normal saline.

Heart rate, non invasive blood pressure and SPO_2 were measured at 2.5 mt interval of the drug injection for the first 20 minutes and thereafter every 10 mt until the end of the surgery. Any decrease in MAP below 20% of the baseline or systolic pressure less than 90mmHg was treated with a bolus dose of ephedrine (6 mg).

Sensory Blockade

Sensory blockade was assessed by pin prick in the mid axillary line at 1 mm intervals until the level of block reached T10. The maximum height of the sensory blockade was noted at 20 minutes. Onset of sensory block was defined as the time taken from injection of drug to sensory block at T 10 and offset of sensory block was assumed when pinprick sensation at the S2 dermatome has returned. Duration of sensory block was defined as the time interval between onset of sensory block at T10 to regression of sensory block to S2.

Motor Blockade

Motor block was assessed by the Modified Bromage score.

0	-	No motor loss
1	-	Inability to flex hip
2	-	Inability to flex knee joint
3	-	Inability to flex ankle

This was assessed at 1 minute interval until complete motor blockade occurred. Onset of motor block was defined as the time taken from injection of drug to development of complete motor block. (Bromage Score-3). Bromage score '0' was considered as complete recovery from motor block. Duration of motor block was defined as time taken from onset of complete motor block to complete recovery of motor block.

Pain

Pain was assessed by an 11 point verbal rating scale (Score 0 - 10) which was explained to the

patient preoperatively. If any patient complained of pain at any time in the intraoperative period, he/ she was given general anaesthesia and was excluded from the study. Post operatively pain was assessed at 2 hour interval for the first 12 hours and then at 4 hour interval for 24 hours. Rescue analgesia in the form of Inj. Tramadol 100 mg IM was given if the pain score was equal to or more than 4. Duration of pain free period was measured from the time of spinal administration of the drug to the time when the patient needed the first rescue analgesia drug. The total number of doses of rescue analgesic requirement in 24 hr was also noted.

Sedation

The level of sedation of the patients was assessed by the Ramsay sedation score.

1 - Anxious and agitated

2 - Co-operative

3 - Asleep but brisk response to loud voice

4 - Asleep with sluggish response to loud voice

5 - No response to loud voice

6 - No response to pain

It was assessed every 15 mm after injecting the drug until the sedation score was 2. All patients were followed after surgery upto 24 hrs for any behavioural side effects, confusion, dizziness, nystagmus, nausea, vomiting or any neurological complications like numbness or pain in the opposite leg, incontinence or retention of bowel or bladder or genital dysaesthesias.

The main end points of our study were

1. Postoperative pain free interval
2. Haemodynamic stability shown in terms of requirement of ephedrine to treat hypotension.
3. Any neurological complication in 24 hrs.

Statistical Tools

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using. Using this software range, frequencies, percentages, means, standard deviations, chi square and 'p values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's test for qualitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

Results

In this randomized double blind study conducted in 90 patients, the subjects were allocated into three groups. All 3 groups were comparable in age, height, weight, duration of surgery. In all the three groups the mean age were comparable and they are not satisfactorily significant. In all the three groups the sex distribution were comparable and they are not satisfactorily significant. In all the three the mean weight were comparable and they are not satisfactorily significant. The ASA physical status in all the three groups were comparable and they are not satisfactorily significant (Table 1).

Table 1: Demographic distribution

Age Group	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
Up to 30 yrs	7	23.3	2	6.7	4	13.3
31 – 40	16	53.3	20	66.7	6	20
41 – 50	5	16.7	7	23.3	10	33.3
> 50	2	6.7	1	3.3	10	33.3
Total	30	100	30	100	30	100
Gender						
Male	24	80	21	70	25	83.5
Female	16	20	9	30	5	16.5
Total	30	100	30	100	30	100
ASA physical status						
I	23	76.7	25	83.3	25	83.3
II	7	23.3	5	16.7	5	16
Range	26-63 yrs		28-60 yrs		23-61 yrs	
Mean	37.93		38.77		41.67	
SD	8.87		6.94		10.6	
'P' Value for	0.1433 Not significant					

Table 2: Onset of Sensory and Motor Block (minutes)

Onset of Sensory Block	Group A Bupi	Group B Bupi/Ket	Group C Bupi/ket/mida
Range	4.5-6.5	3.5-10	3-5
Mean	5.55	7.2	3.92
SD	0.54	2.04	0.5
'P' Value for			
A.B & C		0.0001 Significant	
A & B		0.0033 Significant	
A & C		0.0001 Significant	
B & C		0.0001 Significant	
Onset of Motor Block	**Group A**	**Group B**	**Group C**
Range	7.5-10	7.5-10	5.5-7.5
Mean	8.55	8.55	6.78
SD	0.63	0.63	0.6
'P' Value for			
A.B & C		0.0001 Significant	
A & B		1.0 Significant	
A & C		0.0001 Significant	
B & C		0.0001 Significant	

With addition of midazolam and ketamine the mean onset of sensory block is quicker compared to other two groups. with addition of midazolam and ketamine the mean onset of motor block is quicker compared to other two groups (Table 2).

Maximum sensory level of T4 was reached in 13.3% of cases in Group A. Maximum sensory level of T4 was reached in 13.3% of cases in Group B. Maximum sensory level of T4 was reached in 70% of cases in Group C. With addition of Midazolam and ketamine the maximum sensory level and reached in higher compared to other two groups (Figure 1).

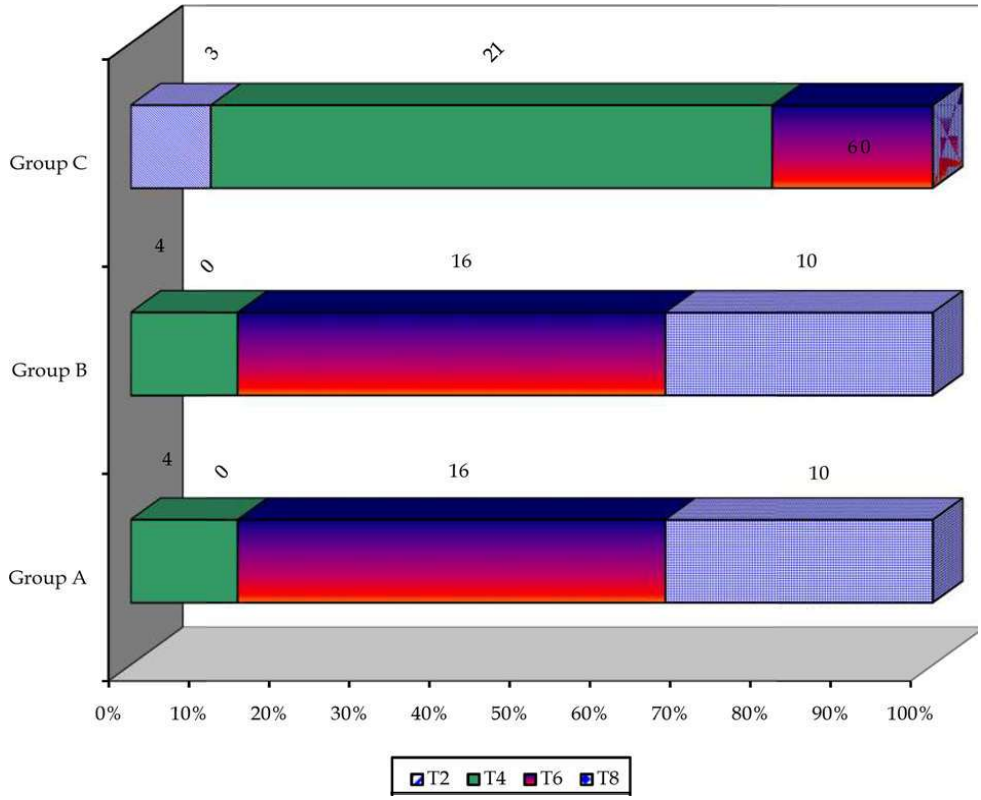

Fig. 1: Maximum Sensory Level

Table 3: Duration of Sensory and motor Block

Onset of sensory Block	Group A	Group B	Group C
Range	160-240	180-280	200-360
Mean	199.7	207	266.3
SD	17.3	21.4	41.6
'P' Value for			
A.B & C		0.0001 Significant	
A & B		1.2436 Not Significant	
A & C		0.0001 Significant	
B & C		0.0001 Significant	
Range	100-180	150-240	160-240
Mean	159.7	181.3	208.7
SD	15.6	20.1	22.7
Duration of Motor Block			
'P' Value for			
A.B & C		0.0001 Significant	
A & B		0.0001 Significant	
A & C		0.0001 Significant	
B & C		0.0001 Significant	

With addition of midazolam and ketamine the duration of sensory block is prolonged compared to other two groups. with addition of ketamine and midazolam the mean duration of motor block is prolonged compared to other two groups (Table 3).

With addition of ketamine and Midazolam the mean duration of pain free interval is prolonged compared to other two groups (Table 4).

With addition of ketamine and Midazolam the number of rescue analgesics required are less compared to other two groups. In all three groups the mean systolic blood pressure was comparable and they are not statistically significant (Figure 2).

Table 4: Duration of pain free Interval (in Minutes)

Duration of pain free interval	Group A	Group B	Group C
Range	240-440	200-360	360-900
Mean	303	296	473
SD	57.4	32.5	136.2
'P' Value for			
A.B & C		0.0001 Significant	
A & B		1.0002 Significant	
A & C		0.0001 Significant	
B & C		0.0001 Significant	

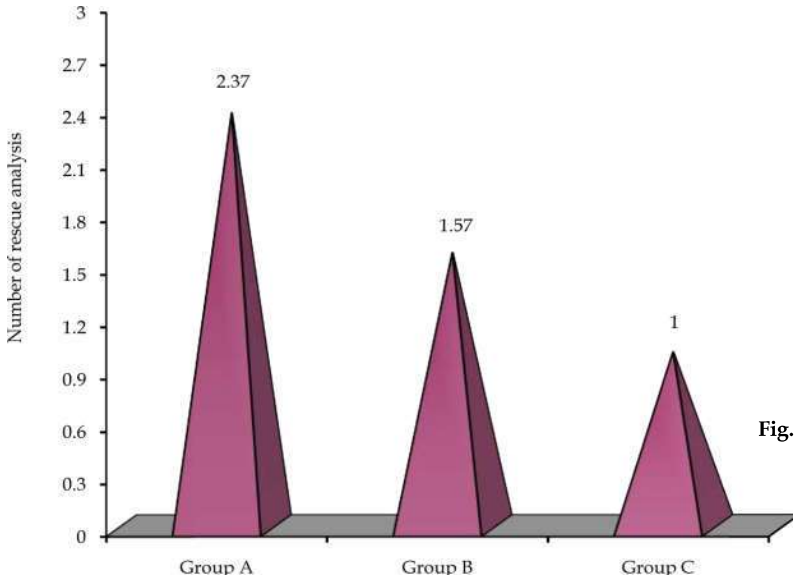

Fig. 2: Number of rescue analgesics

The minimum systolic blood pressure in Group A is comparable to Group C. The minimum systolic blood pressure in Group B and C are not significant and this finding is an added advantage to ketamine midazolam group. In Group B the fall in systolic blood pressure is less comparable to other two groups. (Table 5).

The Vasopressors required in Group A and C were compared and they are not statistically significant. In both these groups the vasopressor requirement was comparable. In Group B the Vasopressor requirement is less compared to other two groups. (Figure 3).

In Group A the range of sedation score was 1-2. In Group B the range of sedation score was 2-3. In Group C the range of sedation score was 2-3. In Group B and Group C the sedation score was higher compared to Group A. (Table 6).

Table 5: Minimum Systolic Blood Pressure

Minimum Systolic B.P	Group A	Group B	Group C
Range	84-110	88-120	80-110
Mean	95.4	104.7	94.9
SD	8.0	8.3	8.0
'P' Value for			
A.B & C		0.0001 Significant	
A & B		0.0002 Significant	
A & C		0.9402 Not Significant	
B & C		0.0001 Significant	

Table 6: Sedation Score

Sedation Score	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
1	5	16.7	–	–	–	–
2	25	83.3	8	26.7	7	23.3
3	–	–	22	73.3	23	76.7
Range	1-2		2-3		2-3	
Mean	1.83		2.73		2.77	
SD	0.38		0.45		0.43	
'P' Value for						
A.B & C			0.0001 Significant			
A & B			0.0001 Significant			
A & C			0.0001 Significant			
B & C			0.7675 Not Significant			

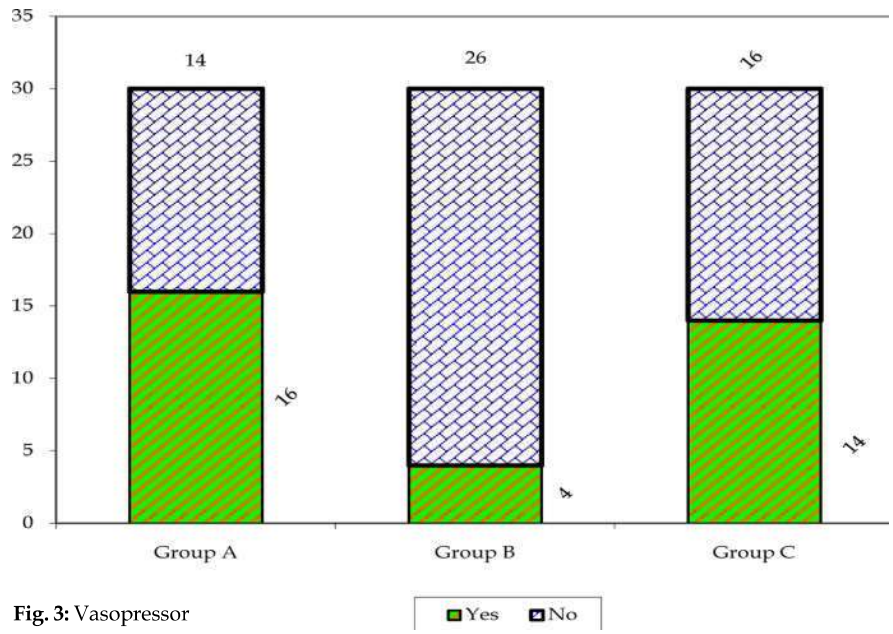

Fig. 3: Vasopressor

Discussion

Ketamine and midazolam are two important anaesthetic drugs which are administered in various routes. Ketamine as slow intrathecal agent was used by Bion and colleagues in 1984 [1]. Kathirvel and colleagues [2] were the first to use ketamine with local anaesthetics intrathecally. Spinal ketamine binds to the phencyclidine site of the NMDA receptor gated calcium channel and inhibits the NMDA receptors non competitively. Its direct axonal blocking effect produces some local anaesthetic activity.

Intrathecal midazolam has been shown to have analgesic properties and potentiates the effects of local anaesthetics. It is an agonist at the benzodiazepine site on a subunit of the pentomeric GABA a receptor. Midazolam tends to suppress afferent evoked excitation in the substantia gelatinosa and motor horn of the spinal cord. Bharti and colleagues [3] had found that postoperative pain Scores were lower in patients who received intrathecal midazolam with bupivacaine.

Kim and colleagues [4] used intrathecal midazolam in doses of 1 and 2 mg along with bupivacaine and found that the duration of postoperative analgesia was significantly prolonged by addition of intrathecal midazolam and was dose dependent.

In this study addition of ketamine and midazolam to bupivacaine (Group C) prolongs the duration of sensory and motor blockade. The mean pain free period was also significantly prolonged. The numbers of reserve analgesics were comparatively less. This finding is consistent with the study done by T. Murali Krishna and colleagues [5] who used low doses of ketamine and midazolam with bupivacaine for orthopaedic surgeries.

In this study addition of ketamine to bupivacaine (Group B) does not alter significantly the time for onset or duration of sensory and motor blockade. The duration of pain free period was also less compared to the midazolam Ketamine group. This finding is consistent with the study done by T. Muralikrishna and colleagues [5], Kathirvel and colleagues [2].

This infers that midazolam in (dose 0.02 mg /kg) when added to ketamine in dose (0.1 mg/kg) and bupivacaine prolongs significantly the duration of post operative analgesia. This might be due to synergistic action of intrathecal midazolam. Ketamine and bupivacaine.

In this study addition of low dose of ketamine with bupivacaine (group B) resulted in stable haemodynamics with decreased incidence of hypotension. This finding is consistent with the previous studies by T. Murali Krishna and colleagues Kathirvel and colleagues and Bion and colleagues [1,2,5]. This may be due to diffusion of ketamine into the venous system of spinal cord which in turn results in cardiovascular stimulation and hemodynamic stability after spinal anesthesia [7,8,9].

In this study the level of sedation was assessed by Ramsay sedation score [6]. The level of sedation at 15 and 30 mm after the block was higher in Group B and C compared to Group A. The maximum level of sedation observed is any patient was 3. No patient required any manoeuvre to maintain airway. Thus intrathecal midazolam and ketamine in low doses had minimal effect on the level of sedation. This finding is consistent with the observation made by T. Murali Krishna and colleagues [5].

Conclusion

From the study it was concluded that low doses of preservative free ketamine (0.1mg/kg) and midazolam (0.02mg/kg) when added to bupivacaine intrathecally provides prolonged post operative analgesia without any significant side effects.

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