



Evaluation of Addition of Low Dose Midazolam to a Mixture of Low Dose Ketamine and Hyperbaric Bupivacaine Given in Subarachnoid Block in Patients Undergoing Lower Limb Orthopaedic Surgery

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Abstract

Background: *Dr Bion used Ketamine first time intrathecally in patients wounded during war time. Intrathecal ketamine produced significant analgesia with stable haemodynamics. Combination of intrathecal Ketamine and Midazolam with Bupivacaine might have the advantages of Stable haemodynamics, prolonged duration of analgesia, synergism could reduce dose requirements, increase therapeutic index and reduce toxicity.*

Aims and Objectives: *To evaluate addition of low dose Midazolam to a mixture of low dose Ketamine and Hyperbaric Bupivacaine in subarachnoid block in patients undergoing lower limb orthopedic surgery to study spinal blockade characteristic, duration and quality of analgesia and side effect profile in addition to post operative analgesia.*

Materials and Methods: *A randomized study was carried out in the Department of Anaesthesiology, Govt. Medical College and SSG Hospital, Baroda between the periods of July 2009 to Feb 2010 with 60 patients, 30 in each group of both sexes.*

Results and Conclusions: *Combination of Ketamine in low dose with Bupivacaine provides stable haemodynamics without any behavioural and central side effects. Addition of Midazolam in low dose to a mixture of low dose Ketamine and Bupivacaine when given intrathecally prolongs the duration of surgical anaesthesia and pain free interval without affecting the other parameters and complications of subarachnoid block.*

Keywords: *Ketamine, Midazolam, Heavy bupivacaine, Subarachnoid block, Intrathecal.*

Introduction

Spinal anaesthesia has many advantages for lower abdominal and lower limb surgeries. Commonly used agents in spinal anaesthesia are Lignocaine and Bupivacaine. Major problems associated with them are hypotension and short duration of post

operative analgesia. Adjuvants used to overcome this problems are Epinephrine, Ketamine, Midazolam, Clonidine, Opioids and Neostigmine. Dr Bion used Ketamine first time intrathecally in patients wounded during war time. Intrathecal ketamine produced significant analgesia with

stable haemodynamics. Higher incidence of central adverse events and poor patient satisfaction limit its intrathecal use. Midazolam has spinally mediated antinociceptive effect. Intrathecal midazolam improves duration and quality of spinal anaesthesia. Duration of postoperative analgesia is significantly prolonged by addition of midazolam intrathecally. Combination of intrathecal Ketamine and Midazolam with Bupivacaine might have the advantages of Stable haemodynamics, prolonged duration of analgesia, synergism could reduce dose requirements, increase therapeutic index and reduce toxicity.

Hence, we planned to evaluate addition of low dose Midazolam (0.02mg/kg) to a mixture of low dose Ketamine (0.1mg/kg) and Hyperbaric Bupivacaine 0.5% (3ml) in subarachnoid block in patients undergoing lower limb orthopedic surgery to study spinal blockade characteristic, duration and quality of analgesia and side effect profile in addition to post operative analgesia.

Our primary aim of this study was to evaluate Pain free interval. While our secondary aims were to evaluate spinal block characteristics and haemodynamic stability as well as to evaluate any post operative complications in terms of behavioral and neurological incidents.

Following parameters were observed for the evaluation: 1) Onset and duration of sensory block, 2) Onset and duration of motor block, 3) Level of sedation, 4) Vital parameters like pulse rate, blood pressure, respiratory rate and oxygen saturation, 5) Duration of pain free interval and analgesic requirement in 24hr post operative period and 6) Side effects occurring during intra and post operative period.

Materials and Methods

A randomized study was carried out in the Department of Anaesthesiology, Govt. Medical College and SSG Hospital, Baroda between the periods of July 2009 to Feb 2010 with 60 patients, 30 in each group of both sexes.

History was taken regarding present and past complaints, personal history, medication history, history of previous anaesthesia exposure, blood transfusion, drug allergy. Neurological disease, etc. general and systemic examination was done. Routine and specific investigations were carried out.

Inclusion criteria included: Patients with age 18-60 yrs, ASA Grade I and II and patients posted for lower limb orthopaedic surgery.

Exclusion criteria included: Patients not willing to participate in study, patients with bleeding disorder, patients with severe deformity of spine, local infection in region of lumbar spine, morbidly obese patients, patients with neurological disease, psychiatric illness, epilepsy in the past, history of drug allergy to drug under study and patients unable to understand pain scales.

All the selected patients were explained about the purpose, procedure and side effects of the study. They were also explained about assessment of pain with the help of Visual Analogue Scale. After this a written and informed consent was taken.

Anaesthetic procedure

Patient was given no premedication. After taking Intravenous line with 18/20 G intravenous cannula, preloading was done with Inj Ringer Lactate 10ml/kg over a period of 20 minutes before giving spinal block. Patients were assigned randomly in one of the following two groups.

GROUP K: patient receiving Inj Hyperbaric Bupivacaine 0.5% 3cc + Inj Ketamine (0.1 mg/kg)

GROUP MK: patient receiving Inj Hyperbaric Bupivacaine 0.5% 3cc + Inj Ketamine (0.1mg/kg) + Inj Midazolam (0.02mg/kg)

All the injection used were preservative free and the solution was made to equal volume of 3.5cc by adding 0.9% normal saline. We used tuberculin syringe to measure exact amount of Ketamine and Midazolam.

After taking the patient in operating theatre, monitors like NIBP (non invasive blood pressure) and pulse oximeter were attached. Base line pulse

rate, blood pressure, respiratory rate, oxygen saturation was noted down.

After checking basic necessities like anaesthesia trolley, resuscitation drugs, and suction apparatus spinal anaesthesia was given using 23 G spinal needle in sitting position. Space chosen and time of drug injection were noted down. Observations were recorded as shown below. Patient having no or inadequate surgical anaesthesia were excluded from the study. Post operatively patient was observed for 24hr for any complications.

Observations

- 1) **Sensory block:** was checked by using pin prick method- Onset of sensory block (at the level of L1 dermatome), Duration of sensory block (time interval from onset to when sensation felt at L1 dermatome again), Duration of pain free interval (time interval from onset of sensory block to when first rescue analgesic given).
- 2) **Motor block:** was assessed by Bromage scale- Onset of motor block (time to attain Bromage grade 3), Duration of motor block (time interval from onset to when Bromage grade become 0 again)
Grade 0: no motor block
Grade 1: unable to flex hip
Grade 2: unable to flex knee
Grade 3: unable to flex ankle
- 3) **Sedation score:** Level of sedation was assessed on four point scoring system
Score 0: No sedation (Awake)
Score 1: Asleep but arousable by using verbal command
Score 2: Asleep and not arousable by using verbal command but responds to painful stimulus
Score 3: unresponsive to painful stimulus
- 4) **Vital parameters:** Pulse rate, blood pressure, respiratory rate, oxygen saturation were monitored. Recording was done before giving block and then at 1, 5, 10 and 15 minutes after giving the block. Then every 15 min till the end of surgery.

- 5) **Duration of surgery:** was also noted
- 6) **Post Operative Period:** Vital parameters were recorded initially at 30 min interval for 6hr then at 1hr interval for 12 hrs. Pain assessment was done every half hourly for initial 6hr then hourly for 24hr by using Visual Analogue Scale (VAS). The duration of effective analgesia or pain free interval was counted from onset of sensory block to when VAS score of 4 or more. At this time, patients were given rescue analgesic Inj Diclofenac Sodium 1.5mg/kg IM. Number and time of rescue analgesic required in 24hr post operative period also noted down.
- 7) **Intra and post operative complications:** Patients were monitored for various intra and post operative complications: 1) Bradycardia: defined as pulse rate less than 20% of preoperative value. It was treated with Inj Atropine 0.6MG IV bolus. 2) Hypotension: defined as systolic blood pressure <20% of pre-procedure value. Inj Mephentermine 5 mg IV bolus given when hypotension occurs. 3) Respiratory Depression: defined as respiratory rate less than 10/min or oxygen saturation less than 90%. It was to be treated with oxygen if required. 4) Nausea and Vomiting 5) Shivering and Rigors 6) Hallucination, emergence phenomenon 7) Post Dural Puncture Headache 8) Backache 9) Urinary retention and 10) Neurological and Behavioral side effects.
- 8) **Analysis of results:** Mean and standard values were taken out. Analysis of variance (ANOVA) of the data for the various parameters was done using student's paired t-test for intra group comparison and unpaired t-test for intergroup comparison. $P < 0.05$ was considered to be significant.

Observations and Results

Table 1: Demographic Data

	GROUP MK (N=30)	GROUP K (N=30)
AGE (YEARS MEAN±SD)	36.92±12.25	30.9±8.42
SEX (M:F)	24:6	23:7
HEIGHT (CM)	166.17±3.57	166.56±5.31
WEIGHT (KG)	55.33±5.71	56.33±4.90
ASA (1 : 2)	30:0	30:0

There were no statistical differences in demographic data between two groups.

The onset of sensory and motor was faster in Group MK. Also duration of sensory and motor

block was prolonged in Group MK compared to Group K. Surgical anaesthesia was adequate in all the cases and there was not a single failure case in either of the two groups.

Table 2: Block Characteristics

PARAMETER	GROUP MK	GROUP K	P VALUE SIGNIFICANCE
ONSET OF SENSORY BLOCK (MIN) (MEAN±SD)	1.99±0.44	3.38±0.66	p<0.001
ONSET OF MOTOR BLOCK (MIN) (MEAN±SD)	6.03±1.13	7.30±1.06	p<0.001
DURATION OF SENSORY BLOCK (MIN) (MEAN±SD)*	151.83±18.29	115.77±13.09	p<0.001
DURATION OF MOTOR BLOCK (MIN) (MEAN±SD)	230.23±29.06	198.07±11.15	p<0.001

Table 3A: Changes in Mean Pulse Rate

TIME	GROUP MK		GROUP K		
	PULSE RATE/ MIN (MEAN±SD)	INTRA-GROUP COMPARISON P VALUE SIGNIFICANCE	PULSE RATE/ MIN (MEAN±SD)	INTRA-GROUP COMPARISON P VALUE SIGNIFICANCE	INTER- GROUP COMPARISON P VALUE SIGNIFICANCE
PRE BLOCK	84.47±7.20		85.47±4.87		p>0.05
POST BLOCK					
1 MIN	84.53±6.89	p>0.05	85.47±4.87	p>0.05	p>0.05
5 MIN	84.40±7.44	p>0.05	85.87±5.97	p>0.05	p>0.05
10 MIN	83.20±8.04	p>0.05	86.20±5.37	p>0.05	p>0.05
15 MIN	82.93±7.37	p>0.05	85.67±5.71	p>0.05	p>0.05
30 MIN	82.80±6.84	p>0.05	85.40±5.46	p>0.05	p>0.05
60 MIN	83.93±6.44	p>0.05	85.33±5.42	p>0.05	p>0.05
90 MIN	84.67±5.95	p>0.05	85.00±5.25	p>0.05	p>0.05
120 MIN	84.67±5.95	p>0.05	85.00±5.25	p>0.05	p>0.05
150 MIN	84.57±5.92	p>0.05	84.80±5.16	p>0.05	p>0.05

This table shows changes in mean pulse rate after giving spinal anaesthesia. In both the groups, the intra-group and inter-group comparison did not

show any significant change in mean pulse rate throughout the study when compared with pre-operative values.

Table 3B: Changes in Mean Systolic Blood Pressure

TIME	GROUP MK		GROUP K		
	SYSTOLIC BLOOD PRESSURE (mmHg) (MEAN±SD)	INTRA-GROUP COMPARISON P VALUE SIGNIFICANCE	SYSTOLIC BLOOD PRESSURE (mmHg) (MEAN±SD)	INTRA-GROUP COMPARISON P VALUE SIGNIFICANCE	INTER-GROUP COMPARISON P VALUE SIGNIFICANCE
PRE BLOCK	119.33±8.23		117.5±7.51		P>0.05
POST BLOCK					
1 MIN	118.63±9.69	P>0.05	117.5±7.51	P>0.05	P>0.05
5 MIN	114.67±9.59	p<0.05	116.37±6.94	P>0.05	P>0.05
10 MIN	111.33±9.88	p=0.001	114.97±6.76	P>0.05	P>0.05
15 MIN	110.67±10.35	p<0.001	114.27±6.18	P>0.05	P>0.05
30 MIN	111.00±9.54	p<0.001	113.67±6.69	P<0.05	P>0.05
60 MIN	112.00±8.60	p=0.001	113.67±6.69	P<0.05	P>0.05
90 MIN	111.00±8.68	p<0.001	113.67±6.69	P<0.05	P>0.05
120 MIN	111.00±8.55	p<0.001	113.83±6.78	P>0.05	P>0.05
150 MIN	111.33±8.68	p<0.001	113.83±6.78	P>0.05	P>0.05

In Group MK the intra-group comparison showed highly significant fall in systolic blood pressure 10 min after giving the block then remained so till the end of surgery. On the other hand, intra-group comparison in Group K showed no significant fall in systolic blood pressure. The inter-group comparison of systolic blood pressure between

Group MK and Group K showed no significant difference throughout the study.

Thus less fluctuation in systolic blood pressure occur in patients of Group K. While patients in Group MK showed significant fall in systolic blood pressure.

Table 3C: Changes in Mean Diastolic Blood Pressure

TIME	GROUP MK		GROUP K		INTER-GROUP COMPARISON P VALUE SIGNIFICANCE
	DIASTOLIC BLOOD PRESSURE (mmHg) (MEAN±SD)	INTRA-GROUP COMPARISON P VALUE SIGNIFICANCE	DIASTOLIC BLOOD PRESSURE (mmHg) (MEAN±SD)	INTRA-GROUP COMPARISON P VALUE SIGNIFICANCE	
PRE BLOCK	76.00±6.75		74.33±8.58		P>0.05
POST BLOCK					
1 MIN	75.87±6.70	P>0.05	74.33±8.58	P>0.05	P>0.05
5 MIN	73.33±8.02	P>0.05	73.33±8.30	P>0.05	P>0.05
10 MIN	70.43±8.68	P<0.05	73.00±8.12	P>0.05	P>0.05
15 MIN	70.33±8.49	P<0.05	72.30±7.58	P>0.05	P>0.05
30 MIN	69.93±7.80	P<0.05	72.20±7.64	P>0.05	P>0.05
60 MIN	69.67±7.65	p=.001	72.20±7.61	P>0.05	P>0.05
90 MIN	70.00±7.88	P<0.05	72.00±7.61	P>0.05	P>0.05
120 MIN	70.00±7.88	P<0.05	72.00±7.61	P>0.05	P>0.05
150 MIN	70.33±7.65	P<0.05	72.00±7.61	P>0.05	P>0.05

The inter-group comparison of diastolic blood pressure between Group MK and Group K showed no significant difference throughout study. Thus less fluctuation in diastolic blood

pressure occurred in patients of Group K. While patients in Group MK showed significant fall in diastolic blood pressure.

Table 4A: Changes in Mean Respiratory Rate

TIME	GROUP MK		GROUP K		
	RESPIRATORY RATE (RATE/MIN) (MEAN±SD)	INTRA-GROUP COMPARISON P VALUE SIGNIFICANCE	RESPIRATORY RATE (RATE/MIN) (MEAN±SD)	INTRA-GROUP COMPARISON P VALUE SIGNIFICANCE	INTER-GROUP COMPARISON P VALUE SIGNIFICANCE
PRE BLOCK	14.60±0.93		14.47±0.86		p>0.05
POST BLOCK					
1 MIN	14.60±0.93	p>0.05	14.47±0.86	p>0.05	p>0.05
5 MIN	14.46±0.86	p>0.05	14.47±0.86	p>0.05	p>0.05
10 MIN	14.50±0.86	p>0.05	14.40±0.81	p>0.05	p>0.05
15 MIN	14.50±0.86	p>0.05	14.40±0.81	p>0.05	p>0.05
30 MIN	14.43±0.82	p>0.05	14.40±0.81	p>0.05	p>0.05
60 MIN	14.43±0.82	p>0.05	14.40±0.81	p>0.05	p>0.05
90 MIN	14.43±0.82	p>0.05	14.40±0.81	p>0.05	p>0.05
120 MIN	14.43±0.82	p>0.05	14.40±0.81	p>0.05	p>0.05
150 MIN	14.43±0.82	p>0.05	14.40±0.81	p>0.05	p>0.05

On intra and inter group comparison, there was no significant change in mean respiratory rate from its pre block value at any given time of study.

Thus respiratory depression as per respiratory rate criteria did not occur in any case in either of the group.

Table 4B: Changes in Mean Oxygen Saturation

TIME	GROUP MK		GROUP K		
	OXYGEN SATURATION % (MEAN±SD)	INTRA-GROUP COMPARISON P VALUE SIGNIFICANCE	OXYGEN SATURATION % (MEAN±SD)	INTRA-GROUP COMPARISON P VALUE SIGNIFICANCE	INTER-GROUP COMPARISON P VALUE SIGNIFICANCE
PRE BLOCK	98.80±0.45		98.67±0.55		p>0.05
POST BLOCK					
1 MIN	98.77±0.47	p>0.05	98.67±0.55	p>0.05	p>0.05
5 MIN	98.73±0.48	p>0.05	98.67±0.55	p>0.05	p>0.05
10 MIN	98.73±0.48	p>0.05	98.70±0.47	p>0.05	p>0.05
15 MIN	98.77±0.47	p>0.05	98.70±0.47	p>0.05	p>0.05
30 MIN	98.79±0.45	p>0.05	98.70±0.47	p>0.05	p>0.05
60 MIN	98.83±0.43	p>0.05	98.70±0.47	p>0.05	p>0.05
90 MIN	98.83±0.43	p>0.05	98.70±0.47	p>0.05	p>0.05
120 MIN	98.83±0.43	p>0.05	98.70±0.47	p>0.05	p>0.05
150 MIN	98.83±0.43	p>0.05	98.70±0.47	p>0.05	p>0.05

On intra and inter group comparison, there was no significant change in mean oxygen saturation from its pre block value at any given time of study.

Thus respiratory depression as per oxygen saturation criteria did not occur in any case in either of the group.

Table 5: Assessment of Sedation

Sedation Score	Group MK	Group K	P Value Significance
Grade 0	4	30	P< 0.001
Grade 1	26	0	P< 0.001
Grade 2	0	0	-
Grade 3	0	0	-

Addition of midazolam to ketamine and bupivacaine provided mild sedation in Group MK patients.

Table 6: Pain Relief

	GROUP MK	GROUP K	P VALUE SIGNIFICANCE
DURATION OF PAIN FREE INTERVAL (MIN) (MEAN±SD)	594±63.39	421.67±38.42	P<0.001
ANALGESIC REQUIREMENT IN 24HR POST OP PERIOD	1.43±0.63	2.4±0.62	P<0.001

The difference was statistically highly significant. Thus addition of midazolam to ketamine and bupivacaine prolong the duration of pain free

interval and decrease the analgesic requirement in post operative period.

Table 7A: Intra operative Complications

INTRA-OPERATIVE	GROUP MK	GROUP K
HYPOTENSION	5	Nil
BRADYCARDIA	Nil	Nil
NAUSEA/VOMITING	Nil	Nil
SHIVERING	Nil	Nil
HALLUCINATION/ EMERGENCE PHENOMENA	Nil	Nil
RESPIRATORY DEPRESSION	Nil	Nil
OTHERS	Nil	Nil

Table 7B: Postoperative Complications

POST-OPERATIVE	GROUP MK	GROUP K
HYPOTENSION	Nil	Nil
BRADYCARDIA	Nil	Nil
NAUSEA/VOMITING	Nil	Nil
SHIVERING	Nil	Nil
HALLUCINATION/EMERGENCE PHENOMENA	Nil	Nil
URINARY RETENSION	Nil	Nil
OTHER BEHAVIORAL AND NEUROLOGICAL COMPLICATION	Nil	Nil

Discussion

Spinal anaesthesia is often used for both elective and emergency lower abdominal and lower limb surgeries. One of the most commonly used local anaesthetic agents in spinal anaesthesia for long surgeries is Bupivacaine. The disadvantage with spinal anaesthesia using bupivacaine alone is a relatively slow onset of action and short duration of post operative analgesia, which means that early analgesic intervention, may be needed in post operative period. Another problem associated with bupivacaine in spinal anaesthesia is hypotension. Efforts have therefore always been made to improve quality, augment the duration of

anaesthesia and analgesia produced by local anaesthetics in spinal anaesthesia with minimal haemodynamic alteration and other side effects.

There is evidence from animal studies that ketamine produce sensory and motor blocks when injected intrathecally. Preservative free ketamine is introduced as a sole spinal anaesthetic agent more than 20 years ago and found to have advantage over local anaesthetic agents in that it provide cardiovascular stability. It was first time used as a sole spinal anaesthetic agent by Dr Bion during war in patients undergoing surgeries for lower limb injuries. Studies by Hawksworth and Serpell, Kathirvel et al, Kaliyani et al showed

psychomimetic disturbances and CNS side effects and thus precluded its use as a sole agent for spinal anaesthesia. Surgical analgesia and motor blocked produced by ketamine is also found to have shorter duration. The amount of ketamine to be added to bupivacaine is also important. Review of literature shows the use of intrathecal ketamine in dose varying from 5-100mg. Studies in which ketamine was used in higher doses such as Kathirvel et al (25mg), Bion JF (5-50mg), Hawksworth and Serpell (0.75-0.9mg/kg), Kaliyani et al (75-100mg), Aloka et al (100mg) were associated with increased incidence of neurological complication like sedation, dizziness, nystagmus and in severe cases emergence reaction. However, Tugal et al and T M Krishna et al used ketamine intrathecally in very low dose 0.1mg/kg and did not come across any side effects with stable haemodynamics with decreased incidence of hypotension. Therefore, in our study we decided to use very low dose of ketamine (0.1mg/kg) with bupivacaine to see whether it provide stable haemodynamic or not and produce any neurological side effects.

Addition of intrathecal midazolam to hyperbaric bupivacaine in various studies Kim and Lee (1-2mg), N Bharti et al (1mg), Nidhi Agrawal et al (1mg), and T M Krishna et al (1mg) clearly shows significant prolongation of post-operative analgesia and pain free interval. N Bharti et al also showed that intrathecal midazolam also improves quality of spinal anaesthesia. There is controversy regarding neurotoxicity of intrathecal use of midazolam in animal studies. A cohort study of 1100 patients by Adam P Tucker et al suggest that intrathecal midazolam in dose up to 2mg did not increase the occurrence of neurologic or urologic complication. He advocated that 0.03mg/kg dose of midazolam was found to be safe. In study by Mi Ja Yun et al, they showed that intrathecal addition of more than 2 mg midazolam require more rigorous attention due to its sedative effect particularly in old and vulnerable patients. Hence, we decided to use midazolam in low and safe dose range 20µg/kg in our study.

Regarding the use of combination of low dose of midazolam and ketamine with bupivacaine, we came across only one study by T M Krishna et al (2008) and we decided to study to evaluate the effect of addition of low dose midazolam to a mixture of low dose ketamine and hyperbaric bupivacaine when given intrathecally in patients undergoing lower limb orthopaedic surgery.

This combination may provide stable hemodynamics with fewer fluctuations in blood pressure and prolongation of pain free interval and may help to overcome this major problems associated with intrathecal use of bupivacaine.

Demographic Data: The two groups are comparable to each other with respect to age, sex, height, weight and ASA status. Furthermore, all the patients included in the study were of ASA 1 status in both groups. Sex ratio M:F is also comparable between two groups.

Block characteristics: The sensory block was assessed in our study by using pin prick method along mid-axillary line. Our result in this regard was in resemblance with those of T M Krishna et al (2008) who also reported significantly quick onset of sensory block in midazolam-ketamine-bupivacaine group as compared to ketamine-bupivacaine group. The quick onset of sensory block indicates synergistic effect between intrathecal midazolam and bupivacaine, though mechanism of action may be different. The local anaesthetic bupivacaine blocks voltage gated sodium channel while midazolam act on benzodiazepine- GABA-A receptor complex at dorsal horn of spinal cord. Thus, combined action of two receptor based system in spinal cord is useful as shown by Tucker et al. Contrary to our study, Nidhi Agrawal et al (2005) in their study showed that no difference in the onset of sensory block by addition of midazolam to bupivacaine.

The duration of sensory block in our study was in resemblance to that of TM Krishna et al (2008) who also noticed significant prolongation of sensory block in midazolam-ketamine-bupivacaine group as compared to ketamine-bupivacaine group. Kathirvel et al (2000) in their

study showed that no significant difference occur in duration of sensory block with addition of ketamine to bupivacaine while Bharti N et al (2003) and Mia JY et al (2007) in their study showed that significant prolongation in duration of sensory block occur with addition of midazolam to bupivacaine.

Reason for short duration of sensory block in Group K may be due to shorter duration action of ketamine as compared to bupivacaine. In Group MK sensory duration prolongation might be because of synergy of action between intrathecal midazolam, ketamine and bupivacaine.

In contrary to our study, Nidhi Agrawal et al (2005) showed no difference in duration of sensory block occur with addition of midazolam to bupivacaine.

Motor Block was assessed by using Bromage score. Onset of motor block was defined as time interval between intrathecal drug administrations to when Bromage grade become 3. The mean time for onset of motor block was 6.03 ± 1.13 min in Group MK as compared to 7.30 ± 1.06 min in Group K. This difference is statistically also significant ($p < 0.001$). All the patients in both group attained Bromage grade 3. Our result is comparable with those of TM Krishna et al (2008), Kathirvel et al (2000) and Bharti N et al (2003).

Duration of motor block in our study was in consonance with that of TM Krishna et al (2008) who also showed prolongation of motor block in midazolam-ketamine-bupivacaine group as compared to ketamine-bupivacaine group. Bharti N et al (2003) in their study also showed prolongation of motor block with addition of midazolam to bupivacaine. Kathirvel et al (2000) in their study showed that duration of motor blockade was shorter in ketamine-bupivacaine group as compared to bupivacaine alone.

Spinal anaesthesia produce sensory, motor and sympathetic blockade. Sympathetic blockade may produce hypotension and changed in pulse rate. There may be bradycardia or tachycardia during surgery. Normally the fall in blood pressure is

within 20% of preoperative value, if the patient is properly hydrated and block is not very high, therefore adequate preloading before giving spinal block is necessary. In our study, we gave injection ringer lactate 10ml/kg for preloading.

As shown by Bion JF, Kaliyani et al and Kathirvel et al intrathecal Ketamine produce stable haemodynamics while Mi Ja Yun et al, N Bharti et al suggest that addition of Midazolam to Bupivacaine does not alter haemodynamics. In our study, addition of midazolam and ketamine in low dose to bupivacaine did not affect the pulse rate significantly.

The mean systolic blood pressure show a significant fall after 10 min of spinal block in Group MK ($p < 0.001$) while no such significant fall observed in Group K. Similarly mean diastolic blood pressure also show significant fall among Group MK ($p < 0.005$) while diastolic blood pressure remain stable in Group K. Our results are consistent with those of T M Krishna et al (2008) who also showed stable haemodynamics with decrease incidence of hypotension in ketamine-bupivacaine group as compared to midazolam-ketamine-bupivacaine group. N Bharti et al (2003) showed that changes in blood pressure and pulse rate were comparable between midazolam-bupivacaine and bupivacaine alone group. Kathirvel et al (2000) also showed that patients in ketamine-bupivacaine group had significantly higher systolic and diastolic blood pressure after induction of spinal anaesthesia and also volume of intravenous fluid required to maintain blood pressure was lower in ketamine-bupivacaine group. Kaliyani et al (2001) in their study also showed that intrathecally administered ketamine caused dose dependent mild increase in pulse rate and systolic blood pressure. Upadhyay et al (1998) in their study also showed that intrathecal ketamine provides stable haemodynamics. Bion JF et al (1984) and Tugal T et al (2004) also showed stable haemodynamic with intrathecal use of ketamine.

It may be due to diffusion of ketamine into venous system (azygous vein) of spinal cord which in turn

results in cardiovascular stimulation and haemodynamic stability after spinal anaesthesia. Midazolam did not prevent the haemodynamic instability produced by intrathecal bupivacaine.

Sedation in our study was assessed by using four point sedation scoring system. No patients in Group K and 4 patients in Group MK had no sedation (Grade 0). While 26 patients in Group MK had Grade 1 sedation i.e. Asleep but easily arousable by using verbal command. Thus, addition of midazolam provided mild sedation in majority of patients in Group MK. In this all cases effect of sedation resolved within an hour.

Our result in this regard is in resemblance to the study of T M Krishna (2008). Yegin et al (2004) also reported sedative scales were significantly higher in bupivacaine plus midazolam group compared to bupivacaine alone group. However, N Bharti et al (2003) and Mi Ja Yun et al (2007) reported that the sedative score were comparable in both groups.

The onset of sedative effects of intrathecal midazolam seemed to slower than intravenous midazolam. It may be due to cephalad spread in CSF or systemic absorption may contribute. In our study, we use ketamine in very low dose 0.1mg/kg which may explain no sedation observed in patients of Group K.

Post operative pain assessment in our study was done by using visual analogue scale. Our results were in consonance with by T M Krishna et al (2008). Kathirvel et al (2000) in their study showed that addition of ketamine to bupivacaine did not provide extended post-operative analgesia or decrease in postoperative analgesic requirements. M H Kim and Lee (2001), N Bharti et al (2003), B Jahangiri et al (2006), Nidhi Agrawal et al (2005) showed in their study that there was significant prolongation of pain free interval and less post operative analgesic requirement with addition of midazolam to bupivacaine. This might be because of synergy of action between intrathecal midazolam, ketamine, and bupivacaine. Analgesic effect of intrathecal bupivacaine was potentiated by intrathecal

midazolam in dose dependent manner as suggested by M H Kim and Lee (2001). Midazolam involved in pain modulation by acting on benzodiazepine receptors in lamina 2 of dorsal horn in human spinal cord. Intrathecal midazolam is also involved in release of an endogenous opioids acting at spinal δ receptors.

In our study we considered hypotension when systolic blood pressure was <20% of pre-block value after spinal injection. In our study 5 patients in Group MK developed hypotension while no patient in Group K had hypotension. Our results are in consonance with the study of T M Krishna et al (2008) who showed no vasopressure required in ketamine-bupivacaine group while 10% of patients in midazolam-ketamine-bupivacaine group required vasopressure to treat hypotension. Kathirvel et al (2000) showed in their study that patients in ketamine-bupivacaine group required less intravenous fluid to maintain blood pressure. No patients from either group had developed bradycardia, respiratory depression, nausea and vomiting, urinary retention and shivering during the intra or post operative period.

Neurological and behavioural side effects were assessed by clinical signs in our study includes pain, motor and sensory deficits, bowel and bladder disturbances, emergence delirium. They were not observed in any of the patients till they were discharged from our hospital. Bion JF (1984), Hawksworth et al (1992), Kathirvel et al (2000), Aloka S et al (2006), Kaliyani G et al (2001) used ketamine in higher doses and showed higher incidence of neurological and behavioural side effects. In our study we used very low dose of ketamine which may be a reason for non occurrence of neurological and behavioural side effects in our study.

Conclusion

Combination of Ketamine in low dose (0.1mg/kg) with Bupivacaine heavy 0.5% (3ml) provides stable haemodynamics without any behavioural and central side effects. Addition of Midazolam in low dose (20 μ g/kg) to a mixture of low dose

Ketamine (0.1mg/kg) and Bupivacaine heavy 0.5% (3ml) when given intrathecally influence the sensory and motor block by shortening the onset time and prolonging the duration of surgical anaesthesia and pain free interval without affecting the other parameters and complications of subarachnoid block.

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