

Original Article:

A comparative study of intrathecal ketamine as an additive to 0.5% hyperbaric bupivacaine for intrathecal anaesthesia

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ABSTRACT

Background: Spinal anaesthesia with bupivacaine for lower limb and lower abdominal surgeries is limited by the fixed duration of action and cannot be prolonged except with usage of spinal catheters which increase the chance of infection and occurrence of haemodynamic instability when used in high doses. To minimize the instability in haemodynamics, several neuraxial adjuvants have been used.

Methods: We carried out a prospective randomized double-blind study in 60 patients posted for lower abdominal and lower limb surgeries. Patients were divided into two groups of 30 each. Both groups received 3 mL of intrathecal hyperbaric 0.5% bupivacaine. In addition, ketamine group (Gr K) received ketamine 0.1 mg/kg body weight intrathecal (made to total volume of 0.5 mL); saline group (Gr S) received equal volumes of 0.9% normal saline intrathecally. The onset and duration of sensory and motor blockade and intraoperative haemodynamics were studied.

Results: Addition of ketamine in comparison to saline administration produced significantly earlier onset (5.2 ± 1 Vs. 3.4 ± 1 ; $p=0.000$), prolonged duration of sensory block (129.7 ± 14.9 Vs. 111.3 ± 11 ; $p=0.000$) and long duration of postoperative analgesia (150.8 ± 11.7 Vs. 127.8 ± 12.8 ; $p=0.000$).

Conclusion: Addition of ketamine to intrathecal hyperbaric bupivacaine provides better intraoperative spinal block characteristics, stable haemodynamics and longer duration of postoperative analgesia.

Key words: Ketamine, Intrathecal, Adjuvant

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INTRODUCTION

Spinal anaesthesia with bupivacaine is administered for lower abdominal and lower limb surgeries with sufficient motor blockade to facilitate the surgeon's work. Bupivacaine also provides effective pain relief in initial post-operative period. Adjuvants like opioids and ketamine are sometimes combined with local anaesthetics for spinal anaesthesia.¹ The rationale for combining adjuvants to local anaesthetic drugs is to lower the dose of each agent, thereby their toxicity and maintain analgesic efficacy while reducing the incidence and severity of side effects.²

Ketamine, a phencyclidine derivative, is a potent analgesic because of its action on nucleus reticularis gigantocellularis in brain stem and by its modest affinity for opioid and N-methyl D-aspartate (NMDA) receptors.³ The advantages of ketamine include a good analgesic effect, cardio-

vascular stability and bronchodilatation in asthmatics.⁴ Ketamine has been used intrathecally in doses ranging from 5-50 mg⁵ for inducing surgical anaesthesia without alteration in patient haemodynamics. With this approach undesirable central effects, such as, drowsiness, hallucinations were observed in more than 50% of subjects. The addition of adrenaline to ketamine results in prolonged duration of motor blockade, maintaining stable haemodynamics but has not decreased the incidence of central effects.⁶ The present study was undertaken to determine whether administration of a lesser dose of ketamine (0.1 mg/Kg body weight) could affect the characteristics of spinal blockade with bupivacaine while minimizing the central effects of ketamine.

MATERIAL AND METHODS

The study protocol was approved by Institutional Research Ethical Committee. Written informed

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consent was obtained from all the patients. The study was a prospective, randomized, single center study included patients admitted for lower abdominal and lower limb surgeries at Sri Venkateswara Institute of Medical Sciences (SVIMS) hospital, a tertiary care teaching hospital in Tirupati, Andhra Pradesh over a period of nine months.

Sixty patients belonging to American Society of Anaesthesiologists (ASA)⁷ physical status I and II aged 18-65 years posted for elective surgeries were included in the study. Patients with infection at the site of spinal injection, patients with ASA physical status III and IV, patients with coagulopathies and those with hypersensitivity to local anaesthetic agents were excluded from the study.

Preanaesthetic evaluation was done one day prior to surgery by anaesthesiologist involved in the study. Patients were explained about the spinal anaesthesia technique and educated regarding the horizontal visual analogue scale (HVAS).⁸ Pre-operative preparation of patients included overnight fasting, premedication with oral alproazolam (0.25 mg) and ranitidine (150 mg). After securing intravenous access using a 18G cannula, the patients were placed in the left-lateral position and 500mL of Ringer's lactate solution was infused over 10 minutes.

The patients were randomly allocated into one of the two groups by computer generated random numbers sequence. Ketamine group received 0.1 mg/Kg of preservative free ketamine made to 0.5 mL along with 15 mg of 0.5% bupivacaine heavy. The saline group patients received 0.5 mL of saline with 15 mg of 0.5% bupivacaine heavy. The study drugs were loaded by an anaesthesiologist who was not involved in the study. Both the patient and anaesthesiologist involved in the study were unaware of study drug composition. The procedural subarachnoid block was done by anaesthesiologist involved in the study with patients in right lateral position with table in horizontal level.

Under strict aseptic, lumbar puncture was performed with No. 25G Quinke spinal needle at L3/4 inter-spinous space using midline approach. Respective drugs were administered over a period of 15 seconds after free flow of cerebrospinal fluid (CSF) was obtained. Patients were immediately returned to supine position and table maintained in horizontal level.

Standard monitoring that included electrocardiogram (ECG), pulse oximetry, respiratory rate and non-invasive blood pressure monitoring was carried out initially and every 1 min for first 10 minutes and then every 5 min thereafter intraoperatively. Hypotension (defined as 20% decrease in systolic blood pressure from base line value) was treated with intravenous fluids and 6 mg boluses of intravenous mephenteramine. Bradycardia (defined as heart rate < 60 beats/min) was treated with intravenous atropine sulphate.

Sensory block was assessed by loss of sensation in response to pin prick. The time to onset of sensory block, maximum level of sensory block achieved and time to achieve maximum sensory block were noted. Intensity of motor blockade was assessed by modified Bromage scale⁹ as follows: Grade 1 complete motor block; Grade 2 able to move feet only; Grade 3 able to move feet and knees; Grade 4 detectable weakness of hip flexion while supine; Grade 5 no detectable weakness of hip flexion while supine; and Grade 6 able to perform partial knee-bend.

No other sedatives or analgesics were administered during surgery. Postoperatively, patients were examined every 30 min for 6 hours to evaluate duration and quality of postoperative pain relief. Pain assessment was done by HVAS⁸ and need for supplemental analgesia was noted. Postoperatively, time to regression to reach L5/S1 level and motor block regression was assessed. Time taken to reach modified Bromage Grade 6 was noted.⁹

HVAS scale for pain is a uni-dimensional measure of pain intensity comprising of a horizontal line,⁸

Cm (100 mm) in length, anchored by two vertical descriptors, one for each symptom extreme (0=no pain; 10=worst pain possible).

Statistical analysis

The data are presented as mean \pm standard deviation (SD). Comparison between two groups with respect to continuous variables like time of onset of sensory and motor blocks was done by student's 't'-test. Categorical variables were compared by Chi-square test.

Changes in magnitude of heart rate and mean blood pressure were divided into four discrete frequency interval groups (0-5 not significant; 5-10 mild; 10-15 moderate; >15 severe) and number of patients falling into each frequency interval was compared by Chi-square test.

All statistical analysis was carried out using the statistical software SPSS 11 software. A p-value less than 0.05 was considered as statistically significant.

RESULTS

The patient characteristics are listed in Table 1. Their mean age (years), anthropometric parameters and duration of surgery were comparable

(Table 1). Sensory block characteristics and motor block characteristics are shown in Tables 2 and 3 respectively. Table 4 shows the changes in magnitude of mean blood pressure (mm Hg) and heart rate difference from the baseline value. Table 5 gives details of mean heart rate difference.

The mean onset of sensory block was significantly earlier in ketamine group ($p < 0.01$). There was no significant difference between the two groups regarding mean time of onset of motor block ($p=0.185$). The height of sensory blockade was between T6-T10 dermatomes; 23 patients in saline group and 22 patients in ketamine group had highest level of sensory blockade at T7 and T8 dermatomes. The mean time of regression (min) of sensory block to L1 dermatome was significantly prolonged in ketamine group ($p=0.000$). There was no significant difference in duration of motor blockade between the two groups ($p=0.14$). The mean duration of complete analgesia was significantly prolonged in ketamine group ($p=0.000$).

DISCUSSION

Subarachnoid block is one of the most preferred anaesthetic techniques for lower extremity and

Table 1: Patient characteristics

Demographic data	Saline group (n=30)	Ketamine group (n=30)	p-value
Age (years)	45.4 \pm 12.5	47.3 \pm 11.5	0.536
Male:Female	21.1	20.10	0.781
Weight (Kg)	60.3 \pm 7.7	58.7 \pm 6.8	0.415
Height (Cm)	164.7 \pm 6.7	163.7 \pm 7.09	0.564

*Data are expressed as mean \pm standard deviation

Table 2: Sensory block characteristics*

Parameter	Saline group (n=30)	Ketamine group (n=30)	p-value
Onset (min)	5.2 \pm 1	3.4 \pm 1.0	0.000
Duration (min)	111.3 \pm 11	129.7 \pm 14.9	0.000
Time to first analgesic administration (min)	127.8 \pm 12.8	150.8 \pm 11.7	0.000

*Data are expressed as mean \pm standard deviation

Table 3: Motor block characteristics*

Parameter	Saline group (n=30)	Ketamine group (n=30)	p-value
Onset (min.)	8.6±1.2	8.2±1.51	0.185
Duration (min.)	159.3±11.9	167±11.6	0.14

* Data are expressed as mean ± standard deviation

Table 4: Mean blood pressure difference

MBP (mm Hg) difference from base line value	Saline group (n=30) No. (%)	Ketamine group (n=30) No. (%)	Significance
0-5	02 (6.7)	20 (66.7)	$\chi^2=14.052$ 0.001
6-10	17 (56.7)	09 (30)	
10-15	08 (22.2)	01 (3.3)	
>15	03 (10)	0	

MBP=mean blood pressure

Table 5: Mean heart rate difference

Difference in heart rate (beats/min) from baseline	Saline group (n=30) No. (%)	Ketamine group (n=30) No. (%)	Significance
0-5	05 (16.7)	16 (53.3)	$\chi^2=24.266$ p=0.001
5-10	17 (56.7)	14 (46.7)	
10-15	08 (26.7)	0	

lower abdominal surgeries because of its simplicity, rapid onset of action and relatively less occurrence of complications. Though it provides intense intraoperative analgesia, this can at most be extended up to immediate postoperative period only. Anaesthesiologists are constantly in a lookout for additive drugs which can prolong the duration of action of local anaesthetics.

As ketamine administration systemically does not induce cardiorespiratory depression⁶ and intrathecal ketamine does not cause neurotoxicity,¹⁰ it seemed worthwhile to investigate possibility of exploiting potent analgesic action of ketamine by co-administering it intrathecally with bupivacaine.

In our study, the mean time of onset and the mean time to reach highest level of sensory blockade were significantly earlier in ketamine group when compared with saline group (Table 2): Similar faster

onset of action of ketamine was noted in other published studies.^{6,11,12} The axonal conduction block produced by ketamine is considered to be partly responsible for this action.¹³ In our study, the mean time of regression of sensory block was significantly prolonged (p=0.000) in ketamine group (Table 2). Similar results were recorded in another study.¹⁴ The longer duration of action of ketamine may be explained on the basis of slow release of ketamine due to liposomal impregnation.¹⁵ This prolongation may also be due to the fact that addition of ketamine to local anaesthetic or any other analgesic in peripheral or neuraxial anesthesia improves or prolongs pain relief (level II evidence).¹⁶

The duration of motor block was almost equal in both ketamine and saline groups (159.33 min Vs 167 min p>0.14). This is in contrast to observa-

tions made in other studies^{15,17} where a relatively less duration of motor blockade was observed when ketamine was co-administered along with lower dose of bupivacaine. In another study⁶ significant prolongation of motor block was noticed in ketamine group by addition of 1 mL of adrenaline (1:10000) to the mixture. Addition of adrenaline to intrathecal ketamine alone has been observed to prolong the duration of motor blockade.^{5,11} The different results observed in our study may have arisen due to the fact that there was no change in the dosing of bupivacaine in both the groups and ketamine has no significant effect over motor blockade on its own.

In our study, the average fall in heart rate from baseline was significantly more in saline group than in ketamine group (Table 5; $p = 0.001$). While 54% of patients in ketamine group had no significant decrease in heart rate, 27% of saline group patients experienced moderate decrease in heart rate (Table 5).

We observed that the average fall in mean arterial pressure was significantly more in saline group (Table 4; $p = 0.001$). The lower incidence of hypotension and bradycardia in the ketamine group can be explained on the basis of property of ketamine to release catecholamines irrespective of dose given.¹⁸

Similar results were obtained in another study¹⁴ where haemodynamic effects of co-administration of ketamine with that of fentanyl was studied. The severity of mean percentage fall in heart rate was more in fentanyl group. A significant incidence of hypotension was also observed in fentanyl group.¹⁴ On comparing bupivacaine with ketamine group, it was observed that though ketamine group was more haemodynamically stable, there was an incidence of bradycardia in 16% of patients in ketamine group.⁶ The addition of intrathecal adrenaline appears to have blocked the centrally mediated cardiovascular effects of ketamine thereby unmasking direct cardio depressant action of ketamine.⁶

In our study there was no incidence of side effects related to ketamine like nystagmus and central sedation. It may be due to the lower dose of ketamine (0.1 mg/kg) used in our study. There was no significant difference between the two groups with respect to other adverse effects like nausea, vomiting and urinary retention. The incidence of nystagmus in ketamine group to be around 40% in another study.¹⁴ This may be due to higher dose of ketamine (25 mg) used in their study. In this study¹⁴ it was observed that while the incidence of vomiting was similar in both groups, the incidence of shivering was more in the fentanyl group. In a study⁶ nearly two-thirds of patients in ketamine group were observed to be drowsy. The authors⁶ reasoned it was because of synergistic action between diazepam premedication and a higher dosage of ketamine (100 mg) employed in study. It has also been postulated that central effects of ketamine limits its usage as spinal additive.¹⁵ This is in contrast to observations made by us wherein we proved the absence of central side effects with minimal doses of intrathecal ketamine.

Surgeries with varying degree of blood loss and duration of surgery may have affected intraoperative haemodynamics in the present study. We did not address the issue of lowering the dose of bupivacaine in the ketamine group so as to verify the intrinsic ability of intrathecal ketamine in a minimal dose to affect the motor power.

Addition of ketamine to intrathecal hyperbaric bupivacaine appears to provide better intraoperative spinal block characteristics, stable haemodynamic and longer duration of post-operative analgesia

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