

*Full Length Research Paper*

# Pharmacological beneficial effect and side effect of intrathecal analgesia, prospective, randomized control trial

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Spinal anesthesia is sufficient to provide adequate motor blockage and also provides effective pain relief during the initial post-operatives period. In order to maximize post-operative analgesia, a number of adjuncts have been added to local spinal anesthetics. The objective of this study is to compare the beneficial and side effects of intrathecal midazolam and ketamine in patients undergoing lower limb surgery. This prospective, open label, parallel assignment, randomized, single-center trial, included eighty patients, who were admitted for lower limb surgery with American Society of Anesthesiologists (ASA) grade I and II between the ages of 20 and 60 years to our hospital were studied for 6 months. From the onsets, intra-operative and post-operative vital signs, pain assessment by visual analogue scale, intra-operative and post operative adverse effects, and post-operative analgesia supplement time were recorded. A significantly higher Visual Analogue Scale (VAS) score were seen in intrathecal ketamine group (Group I) compare to intrathecal midazolam group (Group II). The difference in mean post-operative supplemental analgesic time (Group I:  $482 \pm 68.22$  min, Group II:  $645 \pm 61.28$  min) between the 2 groups was very highly significant ( $p < 0.001$ ). Intrathecal midazolam with bupivacaine provides very good and prolonged post-operative analgesia compare to intrathecal ketamine with bupivacaine. The incidences of side effect are less in Group II compares to Group I.

**Key words:** Analgesia, intrathecal analgesia, ketamine, midazolam.

## INTRODUCTION

Number of adjuncts has been added to local spinal anesthetics to maximize post-operative analgesia. The discovery of enkephalin by Hughes and endorphins by Pert and Snyder in 1975 initiated the opioid receptor theory and studies on pain mechanisms. In 1976, Yaks and Rudy reported the presence of opioid receptors in the spinal cord and they demonstrated that intrathecal administration of morphine produced dose-dependent pain relief in rats. Benzodiazepine receptors are present throughout the nervous system, including the spinal cord.

Midazolam is a water-soluble benzodiazepine with sedative, amnesic, anxiolytic, muscle relaxant, and anticonvulsant properties (Aaltonen and Kanto, 1985; Kanto et al., 1984). Midazolam given by intrathecal or epidural injection can also produce an antinociceptive effect. This may be Gamma-Aminobutyric Acid (GABA) mediated. The Gamma- Aminobutyric Acid has been shown to have analgesic properties. There are many uses for midazolam during the pre-operative period including premedication, anesthesia induction and maintenance of sedation for diagnostic and therapeutic procedures (Audrey, 1998). Ketamine is a potent analgesic that was released in 1968 and is still employed in a variety of clinical settings. Ketamine modulates pain perception at the dorsal horn of spinal cord. N-Methyl-D-Aspartate (NMDA) receptor interaction may mediate general anaesthetic effects as well as some analgesic actions of ketamine (Bullingham and McQuay, 1982).

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**Abbreviations:** CSF, Cerebrospinal fluid; HS, highly significant; SD, standard deviation; VAS, visual analogue scale.

Ketamine is also the only hypnotic agent with analgesic properties. Analgesia induced by ketamine is mediated by the opiate receptors (Fink and Nagai, 1982). The advantages of ketamine include a good analgesic effect, cardiovascular stability in a hypotensive state, broncho-dilatation in asthmatics, and the absence of awareness (Zeisser and Robilart, 1990; Shekaran and Neelakandan, 1996). Disadvantages include increased heart rate and blood pressure, emergence phenomenon, laryngospasm and apnea, increases in intracranial and intraocular pressure, and the lack of visceral anesthesia.

Post-operative pain relief is an unresolved issue. One of the methods of providing post-operative analgesia is by prolonging the duration of intrathecal bupivacaine using additives such as opioid (Tan et al., 2001), ketamine (Upadhyay, 1998; Collins, 1993) or other drugs. The discovery of benzodiazepine receptors in the spinal cord has triggered the use of intrathecal midazolam for analgesia (Batra et al., 1999; Valetine et al., 1996). Intrathecal supplements for post-operative pain relief are intriguing prospects as they eliminate the need for intravenous and intramuscular analgesics and their associated complications. There are only a handful of studies that have assessed the efficacy of the combination of intrathecally administered ketamine and midazolam with bupivacaine.

We performed this study in order to compare the pharmacological benefit and side effects of intrathecal ketamine and midazolam with bupivacaine in patients undergoing lower limb surgery.

## MATERIALS AND METHODS

### Source of data

The study protocol was approved by the Institutional Research Ethical Committee. All patients gave written informed consent. This prospective, open label, parallel assignment, randomized, single-center trial study included eighty patients, who admitted for lower limb surgery to our institution, M.S. Ramaiah Medical College and Hospital, University-Affiliated tertiary care center in Bangalore, India, were studied for 6 months. ASA grade I and II patients between the ages of 20 and 60 years were included in this study. Patients with a history of neurological, coagulation disorders, and known sensitivities to study drugs or emergency surgeries were excluded from the study.

### Pre-operative preparation

Pre-operative assessment was done according to ASA guideline. To the patients the spinal anesthesia technique were explained and educated regarding the Visual Analogue Scale (VAS). Advocated by Revill and Robinson in 1976, the VAS consists of a 10 cm line anchored at one end by the label "no pain" and at the other end with "the worst pain imaginable". The main disadvantage of the VAS is the time required to measure the scale (Godchild and Noble, 1987). The pre-anesthetic preparation of the patients included overnight fasting and pre-anesthesia medication consisting of oral diazepam 0.2 mgkg<sup>-1</sup> the night before surgery. Boyles Anesthesia

machine was checked and a standard intubation kit was prepared. In the operating theatre, the Kits were preloaded with 15 mlkg<sup>-1</sup> intravenous Ringer's lactate solution before administering the subarachnoid block.

### Procedure

Patients were randomly allocated into 1 of 2 groups. Group I (Ketamine) received 25 mg (milligrams) of preservative free ketamine with 10 mg of 0.5% bupivacaine containing 22.5% dextrose made up to a volume of 3 ml with a specific gravity of 1.036. Group II (Midazolam) received 2.5 mg of preservative free midazolam with 10 mg of 0.5% bupivacaine containing 16% dextrose made up to a volume of 3 ml with a specific gravity of 1.035. The specific gravity of spinal anesthetic medication was maintained in both groups. Subarachnoid block was performed with the patients in the right lateral position with the table in horizontal level. With all aseptic precautions using a 23 G spinal needle block was performed at L3-L4 level. Respective drugs were administered over a period of 15 s after free flow of CSF was obtained. Patients were immediately returned to the supine position and the table was maintained in the horizontal level. Standard monitoring was carried out.

Hypotension, defined as a 20% decrease in systolic blood pressure from baseline values [36], was treated with intravenous fluids and 6 mg mephenteramine intravenous boluses. Bradycardia, defined as a pulse rate < 60 min<sup>-1</sup> was treated with intravenous atropine sulphate. The sensory blockage was assessed by the loss of sensation in response to pinprick. The time to onset of the sensory block, maximum level of sensory block achieved and time to achieve maximum sensory block were noted. A dermatomal sensory loss from T<sub>8</sub> to S<sub>4</sub> was considered satisfactory. Intensity of the motor blockade was assessed by the Bromage scale (Bromage, 1981). The duration of surgery for each case was noted. No other sedative or analgesics were given to the patients during surgery. Post-operatively, patients were examined every 30 min for 7 h to evaluate the duration and quality of post-operative pain relief. Pain assessment was determined using the Visual Analogue Scale (VAS). Supplemental analgesia was given when the result of the VAS was greater than 4. The time of supplemental analgesia administration was noted. Following recovery, the ensuing parameters were observed: Time of regression from level L<sub>5</sub> to S<sub>1</sub>, motor power assessed by Bromage scale, and the time of voiding urine, in minutes.

### Statistical analysis

Data are presented as mean ± SD. The results were statistically analyzed by using independent t-test described by Bonferonni. The independent t-test was done to determine the statistical significance between the two groups. In this study, we analyzed the statistical significant differences between Group I (Ketamine) and Group II (Midazolam). The value,  $p > 0.05$  was considered statistically not significant (NS),  $p < 0.05$  was considered statistically significant,  $p < 0.01$  was considered highly significant (HS), and  $p < 0.001$  was considered very highly significant (VHS).

## RESULTS

During the study period, 80 patients were enrolled. Both groups had predominantly male patients, as shown in Table 1. The 2 treatment groups were well-balanced on entry (Table 1). There was no significant difference in the mean onset of action between both groups; group

**Table 1.** Baseline parameter.

Baseline parameter	Group I, n (40) (Ketamine)	Group II, n (40) (Midazolam)	P value
Age: mean (SD) years	49.4 (19)	45.8 (18)	0.7323 <sup>‡</sup>
Male: n (%)	35.00(87.5)	32.00(80)	0.7004 <sup>‡</sup>
Female: n (%)	5.00 (12.5)	8.00 (20)	0.6209 <sup>‡</sup>
Heart rate: mean (SD) bpm	93.30 (7.43)	91.30 (7.84)	0.9128 <sup>‡</sup>
Systolic BP: mean (SD) mmHg	119.78 (10.08)	114.00 (6.68)	0.6272 <sup>‡</sup>
Diastolic BP: mean (SD) mmHg	76.92 (4.51)	76.25 (4.64)	0.5899 <sup>‡</sup>
Respiratory rate: mean (SD) min	13.94 (1.8)	13.80 (2.1)	0.5928 <sup>‡</sup>
Maximum level of sensory blockade T <sub>8</sub> (%)	18.00 (45)	18.00 (45)	0.5309 <sup>‡</sup>
Onset of action: mean mins	8.35	8.67	0.4083 <sup>‡</sup>
Duration of surgery: mean min	120	129	0.4140 <sup>‡</sup>

'P' values of both Group I and Group II more than 0.05, statistically not significant and both groups were well-balanced on entry. \*, No significant differences between the groups at baseline character. ‡, Independent t-test for 2 independent groups was used.

**Table 2.** Intra-operative side effects.

Side effects	Ketamine group, N (%)	Midazolam group, N (%)
Hallucination	2 (5)	-
Vomiting	7 (17.5)	1 (2.5)
Hypertension	2 (5)	-
Rigor	5 (12.5)	5 (12.5)
Giddiness	6 (15)	2 (5)
Sedation	2 (5)	1 (2.5)
Total	24 (60)	9 (22)

Intra-operative side effects between two groups were statistically significant. In Group I, 24 patients (60%) and in Group II, 9 patients (22%) developed side effects. The incidence of intraoperative side effects between the two groups was statistically very highly significant ( $P < 0.001$ ).

I was 8.35 min and Group II was 8.67 min. The maximum level of sensory block as well as the time to onset of action was not statistically significant between groups (Table 1). The average duration of surgery in both groups was nearly equal. In Group I, the average duration of surgery was about 120 min and in Group II, about 129 min. In Group I, 24 patients (60%) developed side effects intra-operatively. Incidence of adverse effects like vomiting, giddiness and rigor were noticed in 17.5, 15 and 12.5%, respectively. In the Group II, only 9 (22%) patients developed side effects and 31 patients did not develop any side effects. The incidence of intra-operative side effects between the two groups was statistically very highly significant ( $P < 0.001$ ) (Table 2). The VAS scores were comparable between both groups during the first 3 h of immediate post-operative period. After 3 h of post-operative period, the VAS score was statistically significant between two groups (Table 3 and 4). In Group II, 32.5% of patients did not require any analgesia within 9 h (Table 4).

A significantly higher VAS score (5 to 6) was observed in Group I from 3 to 6 h post-operatively as compared to

the VAS score (3 to 4) of Group II during this period (Tables 4). In Group I, 5% of patients developed sedation and rigor, and 2.5% patients developed hallucination during the post-operative period. In Group II, 7.5% of patients developed rigor during post-operative period. Post-operative side effects were lesser in Group II compared to Group I (Table 5). Post-operative analgesia was supplemented in all patients in Group I at a mean duration of  $482 \pm 68.22$  min post-operatively ( $p < 0.01$ ; VHS) (Table 6). Only 2 patients in Group II demanded post-operative analgesia within this period. Post-operative analgesia was supplemented in all patients in Group II at a mean duration of  $645 \pm 61.28$  min post-operatively.

The difference in mean post-operative supplemental analgesic time between the 2 groups was very highly significant ( $p < 0.001$ ) (Table 6). The time required for the sensory level to reduce from L<sub>5</sub> to S<sub>1</sub> was longer in Group II compared to Group I ( $p < 0.001$ ). Table 6 shows that the difference in post-operative analgesia effect after regression from L<sub>5</sub> to S<sub>1</sub> level was statistically longer in Group II ( $p < 0.001$ ).

**Table 3.** Visual analogue scale score: Group I (Ketamine).

VAS	Post-operative hours		
	0 – 3 h, n (%)	3 – 6 h, n (%)	6 – 9 h, n (%)
1 – 2	31 (77.5)	1 (2.5)	-
3 – 4	8 (20)	22 (55)	-
5 – 6	1 (2.5)	13 (32.5)	10 (25)
7 – 8	- (32.5)	3 (7.5)	13

A significantly higher VAS score (5 to 6) was observed in Group I from 3 to 6 hours post-operatively (32.5%) compared to Group II (no pain).

**Table 4.** Visual analogue scale score: Group II (Midazolam).

VAS	Post-operative hours		
	0 to 3 h, n (%)	3 to 6 h, n (%)	6 to 9 h, n (%)
1 to 2	38 (95)	5 (12.5)	-
3 to 4	2 (5)	32 (80)	13 (32.5)
5 to 6	-	-	5 (12.5)
7 to 8	-	3 (7.5)	19 (47.5)

In Group II, 13 (32.5%) patients did not require any analgesia within 9 h.

**Table 5.** Post-operative side effects.

Side effects	Group I, n (%)	Group II, n (%)
Hallucination	1 (2.5)	-
Rigor	2 (5)	3 (7.5)
Sedation	2 (5)	-
Total	5 (12.5)	3 (7.5)

Post-operative side effects were lesser in Group II compared to Group I.

**Table 6.** Post-operative parameters.

Parameter	Group I	Group II	t- test	P value	Remark
Mean post-operative analgesia supplement time (SD) minutes	482.25 (68.22)	644.75 (61.28)	8.26	< 0.001	VHS
Sensory regression To L5 – S1 (SD) min	214.25 (40.83)	269.87 (37.9)	6.30	< 0.001	VHS
Voiding of Urine (SD) min	268.72 (43.3)	281.40 (50.3)	1.78	> 0.05	NS
Post-operative analgesia effect after regression to L5 – S1 (SD) min	262.62 (67.63)	334.75 (85.73)	4.00	< 0.001	VHS

SD, Standard deviation; VHS, very highly significant; NS, no significant. The difference in mean post-operative supplemental analgesic time between the 2 groups was very highly significant ( $p < 0.001$ ). The time required for the sensory level to reduce to L5 – S1 was longer in Group II compared to Group I ( $p < 0.001$ ). The difference in post-operative analgesia effect after regression to L5 – S1 level was statistically longer in Group II ( $p < 0.001$ ).

## DISCUSSION

Intra-operative pain, which continues into the post-operative period, is a matter of major concern as far as anesthesiologists are concerned. The importance of

spinal anesthesia with the addition of local anesthesia is well established, as it reduces the severity of post-operative pain and prolongs analgesia even after recovery from sensory and motor blockades. In this study, we compared 2 additives, ketamine and

midazolam, for their analgesic and adverse effects in the post-operative period following spinal anesthesia. Bansal and Bhatia (1994); Ohri (1997) and Upadhyay (1998) concluded that the hemodynamic stability was remarkable with intrathecal ketamine in patients who underwent lower limb and lower abdominal surgeries. In our study, the cardiovascular profile of our patients was found to be stable throughout the intra-operative period in both groups. There was no significant variation in pulse rate or respiratory rate between both groups (Table 1). Bansal and Bhatia (1994) noticed a mild increase in respiratory rate with intrathecal ketamine (mean  $20.8 \pm 0.3$  to  $30.8 \pm 0.4$ ); Bion (1984) did not observe any significant change in respiratory rate, both correlates with our study (Table 1).

Our study shows that the addition of midazolam to intrathecal bupivacaine significantly prolongs the duration of post-operative analgesia. The time to first rescue analgesic was  $645 \pm 61.28$  min in Group II compared to  $482.25 \pm 79.79$  min in Group I. Kim and Lee (2001) reported that the time to rescue analgesic was prolonged by only 2 and 4.5 h when midazolam 1 and 2 mg, respectively, were added to bupivacaine intrathecally. The administration of the benzodiazepine antagonist flumazenil and the GABA-A antagonist bicuculline has been reported to reverse the analgesic effect of intrathecal midazolam, suggesting that the anti-nociceptive actions are mediated via the benzodiazepine, Gamma-Aminobutyric Acid-A receptor complexes, which are abundantly present in lamina II of the dorsal horn ganglia of the spinal cord (Edwards et al., 1990). Intrathecal midazolam probably also causes the release of an endogenous opioid acting on the spinal delta receptor as naltrindole, a delta selective opioid antagonist, suppresses the analgesic effect of intrathecal midazolam (Goodchild et al., 1996). In our study, 38 of 40 patients in Group II did not require any rescue analgesia for more than  $645 \pm 61.28$  min (Table 6). The time of regression from the sensory level of L<sub>5</sub> to S<sub>1</sub> was longer in Group II ( $269 \pm 37.98$ ) compared to Group I ( $214 \pm 40.88$ ). Batra et al. (1999) and Valetine et al. (1996) observed that the mean duration of time to recede from the L<sub>5</sub> to S<sub>1</sub> sensory level was  $267 \pm 67.38$  min, which correlates with our study. The mean post-operative analgesia period after regression from L<sub>5</sub> to S<sub>1</sub> was statistically very highly significant ( $P < 0.001$ ) (Table 6). In Group I, 60% had intra-operative side effects compared to only 22% in Group II (Table 2). The incidence of side effects was more in Group I. In Group I, 42.5% had pain in the first 6 h compared to only 7.5% in Group II ( $p < 0.01$ ) (Tables 2). All patients experienced pain (VAS > 4) in Group I within 9 h, whereas in Group II, 67.5% developed pain (VAS > 4) within 9 h and 32.5% did not require any supplemental analgesia within 9 h ( $p < 0.001$ ) (Tables 3 and 4). We observed superior and prolonged post-operative analgesia in Group II, which was comparable to that observed by Batra et al. (1999).

This study was undertaken to compare the analgesic and adverse effects of intrathecally administered ketamine and midazolam with bupivacaine for lower limb surgery. The quality of analgesia was assessed by VAS. The VAS score was statistically significant between both groups after 3 h of the post-operative period. A significantly higher VAS score was observed in Group I. The incidences of side effect are less in Group II when compared with Group I. In Group I, 42.5% of patient experienced pain in the first 6 h compared to only 7.5% in Group II ( $p < 0.01$ ) (Tables 3 and 4).

## Conclusion

We conclude that intrathecal midazolam provides very good and prolonged post-operative analgesia without significant intra-operative and post-operative side effects compared to intrathecal ketamine.

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