

Research Article

Comparison of efficacy of ketamine, midazolam and ketamine plus midazolam for prevention of shivering under spinal anaesthesia

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ABSTRACT

Background: Ketamine and Midazolam have been reported to be effective for prevention and treatment of post-operative shivering following spinal anesthesia. The present study aimed at the comparison of i.v. ketamine, i.v. midazolam, midazolam and ketamine in combination, and placebo (saline) for the prevention of shivering in patients undergoing elective surgery under spinal anesthesia.

Methods: This study was a double blinded, prospective, randomized controlled study of 120 cases between 18-60 years of age of either sex operated in the Uro-surgery department at KEM Hospital, Mumbai, after obtaining approval from institutional ethics committee and written informed consent from the patients.

Results: Midazolam premedication reduces core body temperature by inhibiting tonic thermoregulatory vasoconstriction whereas, ketamine premedication increased core temperature. Core temperature remained unchanged in combination of the drugs which suggests that the thermoregulatory effects of a benzodiazepine receptor agonist and competitive receptor antagonist of NMDA oppose each other.

Conclusions: This study concludes that use of a combination of ketamine plus midazolam was significantly superior to ketamine alone for the prevention of shivering.

Keywords: Ketamine, Midazolam, Combination, Shivering, Spinal anesthesia

INTRODUCTION

Spinal anesthesia is one of the most popular and safe techniques used for various surgeries. A common problem that develops following spinal anesthesia is shivering. This problem is seen in up to 57% of patients receiving spinal anesthesia.^{1,2} Shivering is a physiologically stressful and undesirable outcome for a patient although its main role is to provide heat. However, its occurrence in relation to anesthesia is not completely understood. It may occur in patients receiving regional anesthesia and some patients recovering from general anesthesia.¹ Shivering can cause several undesirable physiologic consequences, which includes increase in oxygen consumption, carbon dioxide and

minute ventilation. It may induce arterial hypoxemia, lactic acidosis, increased Intra Ocular Pressure (IOP) and affect patient monitoring like Electrocardiogram (ECG), Noninvasive blood pressure (NIBP) and Saturation of peripheral oxygen (SpO₂). Apart from this, it may be detrimental in procedures like fractures and dislocations and can be damaging to patients with low cardiopulmonary reserve.³

Spinal anesthesia decreases the vasoconstriction and shivering thresholds. There is core to periphery redistribution of heat due to spinal induced vasodilation and shivering is preceded by core hypothermia and vasoconstriction above the level of block.^{4,5} The core hypothermia following spinal anesthesia may not trigger

sensation of cold as the cutaneous vasodilation resulting from sympathetic blockade increases skin temperature leading to a sensation of warmth although accompanied by thermoregulatory shivering.⁶

Ketamine is a competitive N-Methyl- D-Aspartate (NMDA) receptor antagonist and has been found to be effective for prevention and treatment of shivering.⁷ It increases arterial pressure, heart rate, and cardiac output because of direct central sympathetic stimulation and inhibition of norepinephrine uptake into postganglionic sympathetic nerve endings, and may decrease core-to-peripheral redistribution of heat.⁸ Thus, it may be logical to use ketamine in patients who are at risk of hypothermia.

Among benzodiazepines, diazepam has been found to be effective in the prevention of postoperative shivering.⁹ Midazolam is another benzodiazepine, which may decrease the incidence of shivering. Midazolam, even in plasma concentrations far exceeding those used routinely, produces minimal impairment of thermoregulatory control.

However, there are few studies regarding the use of midazolam or a midazolam–ketamine combination as a prophylactic agent against intra or postoperative shivering during spinal anesthesia. So, in the quest for safer and efficacious drug choice, this study aimed at the comparison of i.v. ketamine, i.v. midazolam, midazolam and ketamine in combination, and placebo (saline) for the prevention of shivering in patients undergoing elective surgery under spinal anesthesia. The objectives of the study also aimed to compare the sedation score, axillary temperature and tympanic temperature in the four groups, 15 minutes after the spinal anaesthesia has been administered, and to record the vital parameters, in terms of heart-rate, blood pressure, oxygen saturation and side effects, if any.

METHODS

This study was a double blinded, prospective, randomized controlled study of 120 cases operated in Uro-surgery department at KEM Hospital, Mumbai, after obtaining approval from institutional ethics committee and written informed consent from the patients. Patients of 18 – 60 years of age of either sex and belonging to ASA grade I and II undergoing elective surgery under regional anaesthesia were included in the study.

Those who refused to participate, known allergy to ketamine or midazolam, psychological disorders, pregnant patients, cardiopulmonary disease, hypo or hyperthyroidism, initial body temperature >38 or <36 degree Celsius, known history of alcohol/substance abuse, need for blood transfusion during surgery, patients on vasodilators or medication likely to alter thermoregulation and those with ear disease were excluded. These patients were evaluated pre-operatively for their

fitness, for the proposed surgical procedure under spinal anaesthesia. They were kept fasting for 10 to 12 hours.

The selected 120 patients eligible for this study were divided into 4 groups of 30 each.

- Group K - who received Ketamine (K) 0.5 mg/kg i.v.
- Group M - who received Midazolam (M) 75 ug/kg i.v.
- Group KM – who received Ketamine 0.25 mg/kg+ Midazolam 37.5 ug/kg i.v.
- Group Placebo (P)-who received normal saline (NS) 5 ml i.v.

The drug/placebo was given to patients by the investigator according to random number table. However, the observer, who took the readings, was blinded about the drug/placebo given. Lactated Ringer's solution was infused at 10 ml/kg/hr over 30 minutes before administering regional anaesthesia and thereafter, the infusion rate was decreased to 6 ml/kg/hr. Patients were not on any pre-medication.

Heart rate, blood pressure and peripheral oxygen saturation were recorded using standard non-invasive monitors before intra-theal injection and thereafter at 5, 10, 15, 20, 25 and 30 minutes. Before intra-theal injection and at 10 minute intervals during the peri-operative period, body temperature (axillary and tympanic) was recorded.

Axillary temperature readings were taken using a standard electronic thermometer. For assessing tympanic temperature, the subject's head was turned by 30 °C, to one side. The pinna was then pulled up and back. The tip of the electronic temperature probe was put into the ear opening and a button was pressed to switch it on. It was kept in place, till the machine beeped and a reading was shown on the display. The ambient temperature was measured by a wall thermometer and maintained at 24 °C.

Spinal anaesthesia was given at either L3/4 or L4/5 interspaces with hyperbaric Bupivacaine (5 mg/ml) 20 mg using a 23/25 G Quincke's spinal needle. Patients were randomly allocated to receive one of the drug/placebo groups. The treatment drugs were diluted to a volume of 5 ml and presented as coded syringes. All drugs were given as I.V. bolus, immediately after intra-theal injection by an anesthesiologist who was blinded to the group allocation.

Supplemental oxygen (5 liter/min) was delivered via a facemask during the operation. All patients were covered with one layer of surgical drapes over the chest thighs and calves during the operation. During the pre-operative period, sensory block was assessed with a pinprick test at 3 minute intervals. The observer, who was blinded to the study drug, noted the presence of shivering. Shivering was graded using a scale similar to that validated by Tsai and Chu.¹⁰

- 0 - No shivering
- 1 - Pilo-erection or peripheral vasoconstriction, but no shivering
- 2 - Muscular activity in only 1 muscle group
- 3 - Muscular activity in >1 muscle group
- 4 - Shivering involving the whole body

During surgery, the shivering score was recorded at 5 min intervals. If Grade 3 or 4 shivering was noted 15 minutes after spinal anaesthesia and concomitant administration of one of the prophylactic study drugs, the prophylaxis was regarded as ineffective, and i.v. Tramadol 1mg/kg was given. Side effects such as hypotension, nausea and vomiting and hallucinations were recorded. Hypotension was defined as a decrease in MAP of more than 20% from the baseline. This was treated by crystalloid infusion and if necessary ephedrine 6 mg was administered i.v. If patients developed nausea and vomiting, ondansetron 0.1 mg/kg was administered. Hallucination was defined as a false sensory experience where the patient reported they saw, heard, smelled, tasted or felt something that was non-existent.

Degree of sedation was also assessed on a 5-point scale.¹¹

- 1-Fully awake and oriented
- 2-Drowsy
- 3-Eyes closed, but awakening to command
- 4-Eyes closed, but awakening to mild physical stimulation
- 5-Eyes closed, but not awakening to mild physical stimulation.

RESULTS

A total of 120 patients were selected for the study undergoing elective surgery under spinal anaesthesia. Demographic data of the selected patients is presented in Table 1. The mean age of the patients receiving ketamine was 32.83±9.509, of those receiving midazolam was 31.43±10.45 while of those receiving ketamine+midazolam was 32.06±11.52. The mean age of the patients receiving placebo was 32.76±13.91. The difference in the age distribution between the groups was not statistically significant.

Table 1: Demographic data.

Parameter	Ketamine(k)	Midazolam(m)	Ketamine + midazolam (k+m)	Placebo	Statistical test
Age in yrs	32.83±9.509	31.43±10.45	32.06±11.52	32.76±13.91	ANOVA (P=0.07)
Male	23 (77%)	12 (40%)	18 (60%)	18 (60%)	
Female	7 (23%)	18 (60%)	12 (40%)	12 (40%)	
Body weight (in kg)	64.53±5.38	62.86± 6.27	62.33±5.47	60.76 ± 4.01	ANOVA (P=0.06)
Height (in cm)	161.46±4.98	159.3 ±5.93	161.43±5.50	158.5 ± 4.18	Kruskal Wallis test (P=0.07)

Table 2: Parameters studied in different groups.

Parameter	Ketamine(K)	Midazolam(M)	Ketamine + midazolam (K+M)	Placebo	Statistical test
Incidence of shivering at 15 min	No:23	No:16	No:28	No:14	Chi square test (P=0.0003)
	Yes:7	Yes:14	Yes:2	Yes:16	
Sedation score at 15 mins	1.66±0.54	2±0.87	1±0	1 ± 0	Kruskal Wallis test with post hoc Dunn test (P<0.0001)*
Axillary temperature at 10 mins	36.65±0.22	36.2±0.16	37±0.13	36.43± 0.17	Kruskal Wallis test with post hoc Dunn test (P<0.0001)**
Tympanic temperature at 10 mins	36.95±0.29	35.76±0.11	36.69±0.101	35.96 ± 0.16	Kruskal Wallis test with post hoc Dunn test (P<0.0001)***

* Sedation score of the ketamine group is significantly higher than the ketamine and midazolam group (P<0.001); ketamine group is significantly higher than the placebo group (P<0.001); midazolam group is significantly higher than the ketamine (P<0.001); midazolam group is significantly higher than the placebo group (P<0.001). ** The temperature in the midazolam group is significantly lower than the ketamine group (p<0.001); placebo group is significantly lower than the ketamine group (P:0.001); midazolam group is significantly lower than the ketamine and midazolam group (P<0.001); placebo group is significantly lower than the ketamine and midazolam group (P<0.001). *** The temperature in the midazolam group is significantly lower than the ketamine group (P<0.001); placebo group is significantly lower than the ketamine group (P<0.001); midazolam group is significantly lower than the ketamine and midazolam group (P<0.001); placebo group is significantly lower than the ketamine and midazolam group (P<0.001).

Table 3: Various parameters observed in the study among the different groups.

Parameter	Ketamine(K)	Midazolam (M)	Ketamine + midazolam (K+M)	Placebo	Statistical test
Heart rate at baseline	78.13±11.63	80.46±9.33	78.4±11.35	76.8±8.82	Kruskal Wallis test (P=0.71)
Systolic blood pressure (SBP) at baseline	133.86±14.86	131.66±12.96	128.13±12.28	128.46±11.52	Kruskal Wallis test (P=0.104)
Diastolic blood pressure (DBP) at baseline	79.2±9.63	79.2±9.46	77.86±9.02	78±8.18	Kruskal Wallis test (P=0.91)
Mean Blood pressure (MAP) at baseline	97.42±10.69	96.68±10.13	94.62 ±9.84	94.82±9.09	Kruskal Wallis test (P=0.53)
Duration of surgery(in min)	101.33±10.66	99.16±9.92	98.83±11.03	96.33±10.66	Kruskal Wallis test (P=0.59)

77% patients receiving ketamine were males while remaining 23% were females. 60% of patients receiving midazolam were females while 40% were males. 60% of patients receiving ketamine plus midazolam and placebo were males while remaining 40% were females. The mean body weight (in kg) of the patients receiving ketamine was 64.53±5.38, of those receiving midazolam was 62.86±6.27 while of those receiving ketamine+midazolam was 62.33±5.47.

The mean body weight (in kg) of the patients receiving placebo was 60.76±4.01. The difference in the body weights between the groups was not statistically significant. The mean height (in cm) of the patients receiving ketamine was 161.46±4.98, of those receiving midazolam was 159.3±5.93 while of those receiving ketamine plus midazolam was 161.43±5.50. The mean height (in cm) of the patients receiving placebo was 158.5±4.18. The groups were compared using Kruskal Wallis test, the difference in the heights between the groups was not statistically significant.

The incidence of shivering at 15 minutes in the patients is tabulated in Table 2 and as determined by scores when compared by chi square test (p=0.0003) which implies that the incidence of shivering is significantly lower in the ketamine and midazolam group. The values of sedation scores of the groups were analyzed using Kruskal Wallis test with post hoc Dunn test, and it was found that the values were significantly different in the groups (p <0.001). Midazolam group showed highest score among all the groups. The axillary and tympanic temperature at 10 minutes between the 4 groups were studied and are presented in Table 2, analysed using Kruskal Wallis test with post hoc Dunn test. The values observed in the study were significantly different when compared to other groups (p <0.001). However, ketamine plus midazolam showed highest value in both the parameters.

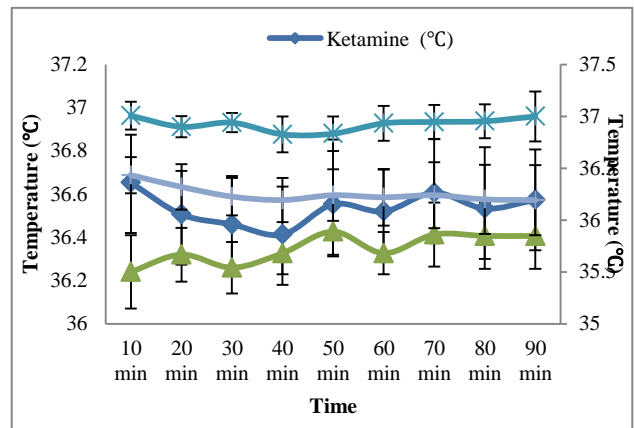


Figure 1: Axillary temperatures of various groups.

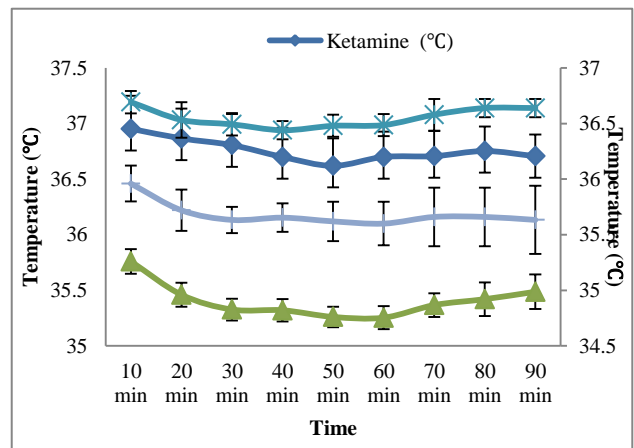


Figure 2: Tympanic temperatures of various groups.

The heart rate, blood pressure and duration of surgery of the four groups were recorded and the data is given in Table 3 in terms of mean±SD. The results were statistically not significant as P value considered <<0.05 is considered as significant.

Table 4: Various side effects observed in between different groups.

Parameter	Ketamine (K)	Midazolam (M)	Ketamine + midazolam (K+M)	Placebo	Statistical test
Incidence of hypotension in the patients (defined by a 20% decrease in the MAP from baseline)	Yes: 3 No:27	Yes:5 No:25	Yes:0 No:30	Yes:8 No:22	Chi square test (P=0.02)
Incidence of nausea and vomiting	Yes: 8 No:22	Yes:3 No:27	Yes:9 No:21	Yes:9 No:21	Chi square test (P=0.21)
Incidence of hallucinations	Yes: 7 No:23	Yes:0 No:30	Yes:3 No:27	Yes:0 No:30	Chi Square test (P=0.0024)

The incidence of hypotension in the patients (defined by a 20% decrease in the MAP from baseline) when compared by Chi Square test gives a p-value of 0.02 which shows the incidence of hypotension is significantly higher in the placebo group and significantly lower in the Ketamine and midazolam group (Table 4). The incidence of nausea and vomiting between the 4 groups when compared by Chi Square test shows a p-value of 0.21 which implies that the incidence of vomiting is comparable between the 4 groups. The incidence of hallucination is significantly higher in the Ketamine group. The 4 groups when compared by Chi square test shows p value of 0.0024 which shows that the incidence of hallucinations is significantly higher in the Ketamine group.

DISCUSSION

Post-anaesthetic shivering adds significantly to the discomfort of the patient in the recovery period. It is not uncommon and can lead to a number of undesirable sequelae. Post anesthetic shivering occurs in 5-65% of patients given general anaesthesia and about 33% of the patients receiving epidural anaesthesia. Post anaesthetic shivering has been defined as readily detectable fasciculation or tremors of the face, jaw, head, trunk or extremities lasting longer than 15 seconds.⁴

A variety of treatment strategies are recommended but there is no clarity about the best option currently available. Shivering can aggravate wound pain by stretching the incisions and increase intra-cranial and intra-ocular pressure. It can increase O₂ demand by as much as 500%. This may lead to a number of complications like arterial hypoxemia, lactic acidosis etc. Minute ventilation and cardiac output increase to maintain aerobic metabolism. This is undesirable especially in the presence of limited cardiac or respiratory reserve.¹² Shivering also interferes with monitoring of the patients as it causes artifacts in the ECG, blood pressure and pulse oximetry.¹³ Risk factors for shivering include male gender, anticholinergic medication and induction agents.⁴

Studies on healthy, human volunteers have shown that normal human core temperature can range between 36.5 to 37.5°C, with mean values consistently 36.9 - 37.0 (0.2 - 0.5°C). Therefore, core hypothermia may be said to commence at 36.4 °C. Though the exact mechanism of shivering during the peri-operative period remains unclear, peri-operative hypothermia has been primarily implicated.¹²

This hypothermia might occur as a protective effect, as it reduces the basal metabolic rate thereby decreasing the risk of tissue hypoxia and ischemia. Shivering might occur as a thermoregulatory response to compensate for hypothermia. During the peri-operative period, hypothermia is controlled by the use of radiant warmers in the operation theatre, warm intravenous fluids and medications to reduce heat dissipation.¹² In addition; skin surface warming and forced air warming systems have been used to prevent peri-operative hypothermia.¹³

Ketamine which is a competitive NMDA receptor antagonist has been found to inhibit post-anaesthetic shivering by its action on NMDA receptors in the hypothalamus or the beta agonist action of norepinephrine. NMDA antagonists have been found to modulate thermoregulation at various levels. Side effects include vivid dreams, extra-corporeal experiences, hallucinations and illusions. These may be overcome with the use of low dose of ketamine.¹³ The patients recruited into this study were similar in terms of age, body weight, height and duration of surgery. This is identical to studies conducted by Honarmand and his co-worker Safavi MR in Iran. According to reports given by Grover et al, little or no effect of midazolam in prevention of post-operative shivering was noted.

Grover et al found that midazolam is ineffective in preventing shivering at the end of the anaesthetic procedure.¹⁴ In present study, shivering was graded using a scale similar to that validated by Tsai and Chu.¹⁰ The incidence of post spinal anaesthesia shivering is significantly lower in the Ketamine plus Midazolam (KM) group (6.6%) in the present study. The Ketamine (K) group showed an incidence of shivering of 23.3%,

the Midazolam (M) group 46% and the Placebo group 53.3%.

This mirrors the findings of Honarmand et al who did a similar study and got an incidence of shivering of 23.3% in the ketamine group, 50% in the midazolam group, 3.3% in the ketamine plus midazolam group and 60% in the placebo group. After 15 minutes of administering spinal anaesthesia, Grade 4 shivering was seen in 2 patients in the M group and 1 patient in the P group. 12/120 patients showed Grade 3 shivering.¹⁵ The results of this study showed that ketamine was superior to placebo or midazolam for prevention of shivering, but the combination of ketamine plus midazolam was definitely better.

Sedation was assessed on a 5 point scale with 1 being fully awake and 5 being unarousable to mild physical stimulation. This is similar to the scale used by Honarmand et al in their study.¹⁵ After administering spinal anaesthesia and before giving the treatment drugs, the sedation score was 1 in all the patients. In this study, the sedation scores of the K and M groups were found to be higher than the P and KM groups ($P < 0.001$ for both). However, the sedation score was higher with M group compared to K group. This is similar to a study conducted in Egypt by Abdelrahman.¹³ This particular study conducted in Egypt also aimed to compare tramadol and tramadol plus ketamine with midazolam and midazolam plus ketamine for preventing post regional anaesthesia shivering.

In this study, the axillary temperature at 10 minutes in the M group is significantly lower than the K group ($P < 0.001$), the temperature in the P group is significantly lower than the K group, temperature in the M group is significantly lower than the KM group.

The lowest axillary temperature was recorded in the M group (36.24°C), followed by the P group (36.43°C). Axillary temperature in the KM group was 37.0°C which was higher than the K group (36.65°C). In a similar study by Honarmand et al, the axillary temperatures increased significantly from the 10th to the 80th minute interval, in the groups receiving midazolam, ketamine and midazolam plus ketamine when compared to the baseline ($P < 0.05$).¹⁵

Core temperature, though it does not completely characterize body heat content and distribution, is the single best indicator of thermal status in humans. It can be measured at the nasopharynx, tympanic membrane, pulmonary artery and distal esophagus.⁶ In this study, authors used tympanic temperature to gauge core temperature, while a similar study by Honarmand et al used nasopharyngeal temperature. In this study, the decreases in core temperature were significantly lower in the groups in which ketamine was used ($P < 0.001$ for both) as compared to the M and P groups. This is similar to the findings of Honarmand et al where the decrease in

core temperature in the ketamine plus midazolam group was significantly less as compared to the other groups ($p < 0.025$).¹⁵

The blood pressure, heart rate and oxygen saturation were comparable between the groups, throughout the study and were not significantly different at any time during the study. In this study, the incidence of hypotension is significantly higher in the P group and significantly lower in the KM group, the incidence of nausea and vomiting is comparable between the four groups and the incidence of hallucinations is significantly higher in the K group. This is similar to studies in the past, such as Honarmand et al where similar doses of ketamine were used with a lower incidence of such reactions.¹⁵

However, this is in contrast to the study by Abdelrahman in Egypt, in which statistical analysis showed no significant differences among the groups with regard to the incidence of hypotension, nausea and vomiting and hallucinations (P-value was 0.0681, 0.240 and 0.456 respectively).¹³ In this study too, a lower dose of ketamine (0.25 mg/kg) in the KM group showed a lower incidence of hallucination (3/30) as compared to plain ketamine group 0.5 mg/kg (7/30).

It is usually ketamine that produces such undesirable reactions, the common manifestations being vivid dreaming, extracorporeal experiences, hallucinations and illusions. It is quite possible that Abdelrahman got such results, due to use of lower doses of ketamine (0.25 mg/kg).

CONCLUSION

To summarize, midazolam premedication reduces core body temperature by inhibiting tonic thermoregulatory vasoconstriction whereas, ketamine premedication increased core temperature. Core temperature remained unchanged when the two drugs were combined. This suggests that the thermoregulatory effects of a benzodiazepine receptor agonist and competitive receptor antagonist of NMDA oppose each other.

The study concludes that use of ketamine is definitely superior to a placebo, for the prevention of shivering in spinal anaesthesia. However, the combination of ketamine plus midazolam was significantly superior to ketamine alone for the prevention of shivering. Addition of midazolam allowed a lower dose of ketamine to be used with a reduction in the incidence of side effects of ketamine.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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