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Original Research Article

Prophylactic use of Midazolam, Ketamine, and Ketamine plus Midazolam for prevention of perioperative shivering during spinal anaesthesia in patients undergoing infraumbilical surgeries: a comparative study

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ABSTRACT

Background: Shivering is a common problem faced by an anaesthesiologist during perioperative period. Shivering occurs during both general anaesthesia and regional anaesthesia but it is more troublesome during neuraxial anaesthesia. To evaluate the effectiveness of intravenous Midazolam, Ketamine and combination of Midazolam with Ketamine in control of shivering.
Methods: The study was conducted in 90 ASA I and II patients receiving neuraxial anaesthesia with comparable dose of hyperbaric bupivacaine. The patients were allocated in three groups of 30 each to receive Midazolam 75 mcg/kg, ketamine 0.5 mg/kg and Midazolam 37.5 mcg/kg plus Ketamine 0.25 mg/kg IV after the appearance of shivering. Disappearance and recurrence of shivering as well as temperature and haemodynamics were recorded with scheduled intervals.
Results: IV Midazolam plus Ketamine at the dose of 37.5 mcg/kg and 0.25 mg/kg is more effective in prophylaxis of shivering than IV Midazolam 75 mcg/kg or IV Ketamine 0.5 mg/kg. Small number of patients showed, clinically as well as statistically insignificant, incidence of hypotension, bradycardia and respiratory depression of various degrees at various time intervals.
Conclusions: Thus, IV Midazolam plus Ketamine at the dose of 37.5 mcg/kg and 0.25 mg/kg IV is more effective in prophylaxis of shivering than IV Midazolam 75 mcg/kg or IV Ketamine 0.5 mg/kg following subarachnoid blockade for infra umbilical surgery. The side effects like Hypotension, nausea, vomiting and pruritus are also very less with combination and prove that it is a better agent for prophylaxis of shivering following regional anesthesia.

Keywords: Ketamine, Medazolam, Shivering, Spinal

INTRODUCTION

Shivering is a relatively common problem encountered perioperatively in regional anaesthesia. Shivering may cause discomfort to patients, and aggravate wound pain by anaesthesia. Shivering may cause discomfort to patients, and aggravate wound pain by stretching incisions and increase intracranial and intraocular pressure. It may increase tissue oxygen demand and accompanied by increase in minute ventilation and cardiac output to maintain aerobic metabolism. This may be deleterious in patients with impaired cardiovascular reserve or a limited respiratory capacity. Shivering also may interfere with the monitoring of patients by causing artifacts of the ECG, blood pressure, and pulse oximetry.[1] Post-anesthetic shivering is spontaneous, involuntary,

rhythmic, oscillating, tremor-like muscle hyperactivity that increases metabolic heat production up to 600% after general or regional anesthesia.[2]

Regional anesthesia is associated with post-anesthetic shivering in up to 60% of patients.[3] Shivering may be normal thermoregulatory mechanism in response to core hypothermia due to redistribution of heat from core to periphery.[4] However, non- thermoregulatory shivering also occurs in normothermic patients.[5]

Post-anesthetic shivering may cause major discomfort to patients and aggravate wound pain by stretching incisions and increase intracranial and intraocular pressure.[6-8] Shivering may increase tissue oxygen demand by as much as 500% and accompanied by increases in minute ventilation and cardiac output to maintain aerobic metabolism. This may be deleterious in patients with impaired cardiovascular reserve or a limited respiratory capacity.[9] Shivering also may interfere with the monitoring of patients by causing artifacts of the ECG, blood pressure, and pulse oximetry recording.

Kurz and colleague, studied the effect of Midazolam on thermoregulation and found that reduction in heat production after administration of Midazolam is less than that after induction of anaesthesia with clinical doses of volatile anaesthetics, propofol, and opioids.[10]

Midazolam is one of the benzodiazepines. It was found that it may decrease the incidence of shivering.[3] Ketamine which is a competitive N-Methyl-D-Aspartate (NMDA) receptors antagonist, has been found to be effective in preventing and treating post-anesthetic shivering via central effects or via its effect on the hemodynamic of the cardiovascular system.[11-13]

METHODS

After obtaining institutional approval and written consent from all patients, this prospective, randomized, comparative study was carried out in UPUMS, SAIFAI, ETAWAH from 2013 to 2016 on 90 ASA status I and II patients who were undergoing elective infraumblical surgery under regional anesthesia. Patients of either sex aged 18-60 years, height between 160±10 cm and Body Mass Index 15-25 kg/m^2 were included.

Unwilling and obese patients, patients with cardiovascular instability, emergency surgeries, drug abuse, allergy to bupivacaine or any study drug, pregnancy, coagulation disorder, spinal deformity, local infection over back or sepsis, abnormal thermoregulation were excluded.

The patients were allocated randomly to one of three groups: Group M (n=30): Midazolam Group, Group K (n=30): Ketamine Group and Group MK (n=30): Midazolam plus Ketamine Group.

The patients were received in the operating theatre, multichannel monitors were attached and baseline values obtained. Intravenous access was established by 18G IV cannula and 500 ml lactated Ringer's solution was infused in 20-30 min for intravenous (IV) hydration. L4-L5 intervertebral space was identified and infiltrated with 1 ml of 2% Lidocaine. Under strict aseptic precautions, lumbar puncture was performed at L3-L4 / L4-L5 interspace through midline approach using a disposable 25-gauge Quincke spinal needle. Immediately after the subarachnoid block study drugs were given in the following doses.

- Group M (n=30): received Midazolam 75 mcg/kg body weight
- Group K (n=30): received Ketamine 0.5 mg/kg body weight
- Group MK (n=30): Received Midazolam 37.5 mcg/kg plus Ketamine 0.25 mg/kg body weight.

All of these drugs were diluted to volume of 5 ml and was given as an I.V. bolus immediately after intrathecal injection by an anaesthesiologist who was blinded to group allocation. Supplemental oxygen was given via a face mask at a rate of 3 L/min during the operation. All patients were covered with one layer of surgical drapes over the chest, thighs and calves during the operation and one cotton blanket over the entire body after the operation.

When spinal anesthesia was established the presence of shivering was observed by an observer blinded to the study drug administered. Shivering was graded by using a scale similar to that validated by Tsai and Chu where Grade 0 is no shivering and Grade 4 is shivering all over the body.[14]

The score was evaluated during surgery and if shivering occurred, it was graded and recorded. If the grade was 3 or 4 after 15 minutes from the administration of the tested prophylactic drug, it was considered severe shivering and rescue treatment in the form of I.V. 25 mg Tramadol was given.

The degree of sedation was assessed according to a five-point scale. Systolic and diastolic blood pressure, mean arterial pressure and heart rate were recorded at 5 minutes interval for first 30 minutes and thereafter t at intervals of 10 minutes for the rest of intra operative period. In the Post Anaesthetic Care Unit (PACU) vital signs were recorded every 20 minutes for up to 3 hours 30 minutes after giving spinal. Hypotension was treated with crystalloid I.V. and a bolus dose of I.V. atropine was given intravenously (600 μg) if heart rate became less than 50 beats per minute. Requirement of these drugs with doses were also recorded. Any other side effect was recorded and properly treated e.g. nausea, vomiting and hallucination. Patients were monitored postoperatively up to 24 after surgery and time taken for complete loss of

effect of spinal anaesthesia observed. They were also observed for any episode of recurrence of shivering.

Statistical analysis

Data were recorded, summarized, tabulated and statistically analyzed using SPSS Statistics program (Version 17).

Statistical presentation and analysis of this study was conducted, using the mean, standard deviation (SD), analysis of variance (ANOVA) test and Chi-square test to examine difference among the three groups as regard the parametric variables. P-value < 0.05 was considered significant.

RESULTS

The groups were comparable in respect to demographic parameters, distribution of different types of surgeries performed and mean duration of surgery (Table 1).

Incidence of shivering was lowest in Group MK. While efficacy of Ketamine alone was found to be better than Midazolam but the incidences of shivering were comparable in these groups (Table 2 and 3).

Table 1: Demographic data, ASA status and duration of surgery.

	Group M N=30	Group K N=30	Group M+K N=30	P value ANOVA	
Age (years)	41.433±18.214	42.933±14.8020	41.700±12.2084	0.921	
BMI (Kg/m^2)	20.409±2.115	19.936±2.810	19.809±2.536	0.622	
Duration of surgery (min)	60.500±18.952	69.433±12.5112	68.467±15.5668	0.063	
Sex (M/F)	28/2	27/3	28/2	Chi squared	
				X2	P value
				0.3098	0.856
ASA (1/2)	30/0	30/0	30/0	NA	NA

BMI = Body Mass Index; NA = Not Applicable; Values of sex are expressed as number of patients

Table 2: Incidence of shivering in three groups.

	Group M N=30	Group K N=30	Group K+M N=30	Chi square	
				X2	P
Shiverer	17 (56)	10 (33)	2 (7)	17.962	0.000184
Nonshiverer	13	20	28		
Comparison between Group M and Group K				3.2997	0.069
Comparison between Group M and Group MK				17.3299	0.0031
Comparison between Group K and Group MK				3.678	0.011806

Table 3: Shivering of grade ≥ 3 in three groups.

Shivering score	Group M	Group K	Group MK	Chi square	
				X2	P
≥3	4 (13%)	2 (7%)	1 (3%)	2.168	0.338126
<3	26	28	29		

Table 4: Intraoperative complications.

Complication	Group M	Group K	Group MK	Chi square	
				X2	P
Hypotension	5 (17%)	2 (7%)	4 (13%)	1.4499	0.484339
Hallucination	0	4 (13%)	1 (3%)	5.5059	0.06374
Nausea	3 (10%)	4 (13%)	0	4.0275	0.133
Vomiting	0	5 (17%)	4 (13%)	5.033	0.123

Though small number of patients showed incidence of hypotension, bradycardia and respiratory depression of various degree at various time intervals but were found to be clinically as well as statistically insignificant. In Group K mean arterial pressure (MAP) and heart rate (HR) were maintained at slightly higher level throughout

the study period in almost all of the cases. Moreover, patients from group K and group MK showed a higher sedation score than group M. The incidences of nausea, vomiting, pruritus was less in group MK than other two groups (Group M and Group K). However, the dream like state was more frequent in Group K but all findings were statistically insignificant (Table 4).

DISCUSSION

The demographic profile, height, weight etc. were comparable across the groups (Table 1). The types and duration of surgery were also comparable between the groups. We kept the temperature of OT and recovery room constant at 23-24˚C and the patients were infused IV fluids after prewarming at about 37ºC by hot water tub.

The average time taken for onset, level and intensity of subarachnoid block was also comparable across the groups. Hence there was no effect in incidence of shivering due to variation in extent of block.

Present study shows (Table 2) that out of 30, 17 patients in Midazolam Group (Group M), 10 in Ketamine Group (Group K) and 2 in Midazolam plus Ketamine Group (Group MK) experienced shivering of various grades. This difference was seen within 15 minutes after spinal anaesthesia. Thereafter and even in postoperative period, incidence of shivering was statistically comparable. 56% patients of Group M suffered shivering as compared to 33% incidence of shivering in Group K. Though the incidence seems to be clinically significant but statistically insignificant (p value 0.069) in both M and K groups, the incidence was only 7% in Group MK which is highly significant even statistically.

Honarmand et al, compared the prophylactic use of midazolam, ketamine, ketamine plus midazolam and placebo for prevention of shivering during regional anesthesia, and found that the shivering incidence was 50% of the midazolam group, 23.3% in ketamine Group and 3.3% in midazolam plus ketamine Group.[3]

This was similar to the midazolam group (Group M) of the current study shivering occurred in 56% of patients (17/30) which was lower and statistically significant in ketamine group (33%) and ketamine plus midazolam group (7%).

Also, the incidence of severe shivering (score≥3) is non-significant in this study which is in accordance with the observations made by us (Table 3).

Abdelrahman RS also showed that that the incidence of shivering was less in Group MK (5%) as compared to Group M (45%) while using similar doses. This is comparable to the incidence of shivering in these 2 groups in the present study. He also concluded that the Group MK is better than Group M.

In similar study in the year by Sagir et al, compared placebo, Ketamine, Granisetron, and a combination of Ketamine and Granisetron for the prevention of shivering caused by regional anesthesia, and found that 55% of the patients in placebo group suffered from shivering of various grades after subarachnoid block with inj. bupivacaine.[12] But this incidence of shivering was reduced to zero in ketamine group in his study. While the present study shows 33% incidence in Ketamine group. But out of these 33% most of the patient suffered from shivering of Grade 1 or 2 only, while the clinically significant grade 3 shivering was found only in 2 cases out of 30 (7%). This could be due to the colder airconditioned OT in our hospital.

Tariq MA in double blinded randomized controlled study 200 patients listed for urologic surgery were randomized in two groups of 100 patients each.[16] The patients were randomly allocated to receive ketamine 0.25 mg/kg plus midazolam 37.5 µg/kg or ketamine 0.5 mg/kg. After 15 minutes, the incidences of shivering in groups A and B were 4% and 25%. While in the present study it was 6% and 24% respectively. The number of patients with a shivering score of ≥3 was significantly higher in group B compared with groups A (4 versus 0, respectively).[16]

Kurz et al, studied the effect of midazolam on thermoregulation and found that reduction in heat production after administration of midazolam is less than that after induction of anesthesia with clinical doses of volatile anesthetics, propofol, and opioids.[10] Also, they reported that midazolam, even in plasma concentrations far exceeding those used routinely, produces minimal impairment of thermoregulatory control.

In the present study 13% patient showed hypotension in Group MK (Defined as MAP <100 mmHg or less than 20% than preoperative baseline value) and no incidence of bradycardia (heart rate <50 bpm). Inj mephentermine was used as rescue drug for hypotension. These findings are same to Sagir O et al, reported incidence of hypotension 5-23% in different groups. They used inj. ephedrine for the patients with hypotension.

In the present study, the intergroup comparison showed that MAP and heart rate were more during the perioperative period in Group K than Group M and Group MK ($p < 0.05$) which is statistically significant. This may be due to the intrinsic sympathomimetic activity of ketamine which was absent in the other two study drugs. However, none of our patient had tachycardia (H.R. >100 /min) or hypertension (BP >140 /90), findings of the present study corroborate well with the findings of Sagir O et al.[12] In the present study the incidence of hypotension was 16% in midazolam, 7% in ketamine, 13 % in ketamine plus midazolam group. These findings are similar to the study done by Abdelrahman RS on prevention of shivering during regional anaesthesia.[15] The incidence of hypotension in

this study was 15% in midazolam group and 5% in midazolam plus ketamine group.

The sedation score of more than 1 was more in Group M (11/30) as compare to Group K (7/30) and Group MK (5/30). In this connection, the patients of Group K and Group MK have more perioperative comfort than group M. The grade 5 shivering was not seen in any of the patient. This finding of present study corroborates well with the study by Sagir O et al.[12] They reported increased sedation and better perioperative comfort in the patients with ketamine pretreatment.

No incidence of hypoxia and hypoventilation was observed in present study. Inspite of the fact that sedation by Midazolam and Ketamine reduce respiratory rate and tidal volume, none of the patient showed any incidence of desaturation.

CONCLUSION

From the observations and analyses of the present study, it can be inferred that:

- IV Midazolam plus Ketamine at the dose of 37.5 mcg kg^{-1} and 0.25 mg kg^{-1} IV is more effective in prophylaxis of shivering than IV Midazolam 75 mcg kg^{-1} or IV Ketamine 0.5 mg kg^{-1} following subarachnoid blockade for infra umbilical surgery.
- The side effects like Hypotension, nausea, vomiting and pruritus are also very less with combination and prove that it is a better agent for prophylaxis of shivering following regional anesthesia.
- Better hemodynamic stability, adequate sedation with Ketamine plus Midazolam has made it an acceptable alternative than Midazolam and Ketamine in this regard.
- Perioperative saturation oxygen, postoperative consciousness, urinary retention and post dural puncture headache are not affected by pretreatment with our study drugs.

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