ORIGINAL ARTICLE OPEN ACCESS

Comparison of Pre-emptive Usage of Ketamine and Combination of Ketamine With Midazolam to Prevent Shivering During Neuraxial Block

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ABSTRACT

Objective — *To evaluate the effectiveness of pre-emptive usage of intravenous ketamine and combination of ketamine with midazolam to control shivering during neuraxial block.*

Study design — *Comparative study.*

Place & Duration of study — *Department of Anesthesiology, Surgical Intensive Care Unit and Pain Management, Dr. Ruth K.M Pfau Civil Hospital Karachi (CHK), from May 2015 to October 2015.*

Methodology — *Patients were divided into two groups. Group K received ketamine 0.5mg/kg and in group KM, ketamine 0.25mg/kg and midazolam 37.5 microgm/kg were given. Just after subarachnoid block, all study drugs were administered through intravenous route as bolus dose. Data were entered into a predesigned form. Data analysis was done with SPSS version 17. Chi square test was applied for statistical significance.*

Results — *The mean age of the patients was 36.12±6.78 year. There were 73 (81.1%) male and 17 (18.9%) female patients. Rate of postoperative shivering was significantly low in group KM as compared to group K (13.3% vs. 64.4% - p=0.005). Side effects of ketamine were also less in KM group.*

Conclusion — *The combination of reduced dose of ketamine plus midazolam was superior to ketamine alone in preventing shivering during spinal anesthesia.*

Key words — *Shivering, Ketamine, Midazolam, Spinal anesthesia.*

INTRODUCTION:

Involuntary and continuous movement of one or more skeletal group of muscles occurring after neuraxial block or general anesthesia is called as shivering.[1] Regional anesthesia diminishes thermoregulation and up to 57% incidence of shivering has been reported during neuraxial anesthesia.[2] For the treatment of shivering warming equipment and drugs are used. In literature various groups of drugs are recommended for shivering like serotonin receptor blocker, opioids, cholinomimetics, benzodiazepine, neostigmine etc.[3] Shivering increases expenditure of oxygen and increases carbon dioxide production.[3] Shivering patients develop ECG changes, rise in intracranial and intraocular pressure, increased body metabolism and acidosis.[4,5] Regional anesthesia facilitates redistribution of heat from periphery to central body compartment due to vasodilatation.

Ketamine has a role in thermoregulation by acting competitively on receptors.[7] It controls shivering by blocking beta-adrenergic effect of nor epinephrine.[8]

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Sagir et al found pre-emptive dose of ketamine 0.5mg/kg as efficacious but patients may develop side effects.[9] Midazolam used in routine doses produces minute change in thermoregulatory control.[10] Honarmand and Safavi compared ketamine plus midazolam with ketamine alone in spinal anesthesia and observed decrease in shivering in ketamine midazolam group and found it useful.[7] However it caused side effects mainly hallucination, psychosis, nausea and vomiting after the procedure. This study was conducted to compare the effect of ketamine with the combination of reduced dose of ketamine and midazolam during neuraxial anesthesia so as to document effectiveness of this combination without producing side effects.

METHODOLOGY:

A comparative study was conducted in the Department of Anesthesiology, Surgical ICU and Pain Management, Dr Ruth K.M Pfau Civil Hospital Karachi, from May 2015 to October 2015. Approval of study was obtained from Ethical Review board of Dow University of Health Sciences. This was also approved by the College of Physicians & Surgeons Pakistan. Patients between 18 years to 50 years of either gender, American Society of Anesthesiologists (ASA) physical status I and II, planned to undergo lower abdominal surgeries, gynecological and orthopedic procedures on lower limbs, were included. Patients suffering from thyroid disorders, cardiac and pulmonary diseases, psychiatric disorders, alcoholics, patients requiring blood transfusion, body temperature above 38.0^{0}C or less than 36.0^{o}C, and history of medications altering thermoregulation were excluded.

Sample size was calculated with the help of WHO calculator, ketamine response rate [7] of 23.3% and ketamine plus midazolam response rate[7] of 3.3% by keeping confidence interval (CI) 95% with Power of 80% the sample size (n) calculated was 90 patients (45 in each group). Informed and written consent was taken from the patients. They were explained about the potential risks and benefits of the study drug.

In operating room, all patients received an 18G intravenous cannula. Crystolloid solution warmed to 37^{o}C was given at the rate of 10-15 ml/kg in 20 minutes before the neuraxial block. Pulse rate, mean arterial pressure (MAP), and oxygen saturation (SpO_2) were noted before subarachnoid block and every 5 minutes after block up to 30 minutes. Body temperature was recorded with a thermometer in axilla before spinal block and during the procedure at 15 minutes intervals. Neuraxial anesthesia was performed at either L3/4 or L4/5 space. Hyperbaric bupivacaine 10mg to 12mg was given by 25 G cutting type-Quincke spinal needle. Patients were randomly assigned to the following groups by envelope method: Group K received ketamine 0.5 mg/kg, Group KM received ketamine 0.25mg/kg plus midazolam 37.5 microgm/kg. Just after subarachnoid block, all study drugs were administered as bolus dose. The treatment drugs were presented as coded syringes by an anesthesiologist. Shivering was measured by Tsai and Chu Scale.[11] Effectiveness was measured in terms of no shivering after 90 minutes.

Data entry and statistical analysis were done using statistical package of social sciences SPSS version 17. Mean and standard deviation was calculated for all the quantitative variables like age, weight, height, and duration of surgery. Relevant descriptive statistics like percentages and frequencies were calculated for all the qualitative variables like gender, effectiveness, ASA status, type of surgery and co-morbid conditions. Chi square test was applied to compare the efficacy of group K and group KM at 5% level of significance. Stratification was done to control effect modifiers. Post stratification Chi square test was applied to find out significance level.

RESULTS:

The mean age of patients was 36.12±6.78 year (95% CI: 34.7 -37.54). Mean age, height and weight of the patients were not significant between groups (table I). There were 73 (81.1%) male and 17(18.9%) female patients. Out of 90 patients, ASA-I status was observed in 59 (65.6%), and ASA II in 31(34.4%) cases. Diabetes mellitus and hypertension were present in 26 (28.9%) and 34 (37.8%) patients respectively.

The rate of shivering in group KM was 13.3% and in group K 64.4%. Rate of postoperative shivering was significantly low in group KM as compared to group K as shown in table II. The frequency of hypotension, nausea, vomiting, hallucinations and muscle rigidity are reported in table III. Patients who developed hypotension were treated with ephedrine 6 mg IV. Four (8.8%) patients had muscle rigidity in K group as compared to KM group in which 02 (4.4 %) patients suffered from this symptom.

DISCUSSION:

Spinal anesthesia is a safe anesthetic technique for many surgical procedures. Around 40-60% of the patients develop shivering after subarachnoid bock.[12] Intraoperative shivering is very troublesome and physiologically frustrating. In patients with coronary artery disease, it may cause ischemia because of

Table I: Comparison of Variables Between Groups

Variables	Group KM n=45	Group K n=45	P-Values
Age (Years)	35.38±6.99	36.87±6.86	0.300
Weight (kg)	143.38±11.39	144.87±13.43	0.572
Height (cm)	60.04±4.45	59.2±5.63	0.432

Table II: Comparison of Effectiveness Between Groups

Effectiveness	Group KM n=45	Group K n=45	Total n=90
Effective (Shivering Absent)	39 (86.7%)	16 (35.6%)	55 (61.1%)
Ineffective (Shivering Present)	6 (13.3%)	29 (64.4%)	35 (38.9%)

Chi-Square value=24.73 P= 0.0005

Table III: Frequency of Side Effects

Side Effects	Group KM n=45	Group K n=45
Hypotension	3 (6.6%)	1 (2.2%)
Nausea and vomiting	7 (15.5%)	9 (20.0%)
Hallucinations	3 (6.6%)	5 (11.1%)
Muscle rigidity	2 (4.44%)	4 (8.8%)

increase in oxygen consumption of up to 6%.[13] These problems can lead to neurological deficits and cardiovascular compromise as well as organ failure. It may produce deleterious impact on disease outcomes, patient recovery, and hospital stay. It also impedes oxygen monitoring and electronic devices, which may be hazardous.[14,15]

Various drugs are studied but benchmark drug has not been found yet. In this study the pre-emptive use of reduced dose of intravenous ketamine with midazolam showed promising outcome. It appears that ketamine is likely to affect the thermoregulation through certain mechanisms.[7,16] It is reported that ketamine reduces central to peripheral heat distribution by preventing the vasodilatation that occurs under anesthesia.[17] Additionally it is hypothesized that ketamine may control shivering by interfering with thermoregulatory mechanism within central nervous systm.[15] The rate of shivering in group K was found to be 64.4% in index study. Ketamine in a dose of 0.5 mg/kg was found to be effective in preventing shivering.[9] Dal et al and Gangopadhyay et al highlighted the role of ketamine under general and spinal anesthesia respectively though side effects are also reported.[16,18]

Midazolam is another benzodiazepine that may decrease the incidence of shivering. In our study patients in group KM were treated with ketamine plus midazolam. We found that the rate of shivering in group KM was 13.3%. Our data suggested that combination of drugs helped in avoiding the element of shivering by inhibiting arteriovenous vasodilation.[19] It can be deduced that the mixture of midazolam and ketamine enhanced mutually the anti-shivering effect thus a synergistic effect occurred when two drugs were combined. Further studies are needed to find out the precise mechanism of interaction.

CONCLUSIONS:

The combination of reduced dose of ketamine and midazolam was superior to ketamine alone in preventing shivering that developed during subarachnoid block. Addition of midazolam allowed a lower dose of ketamine to be used with a reduction in the side effects of ketamine.

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Received for publication: 21-09-2020

Accepted after revision: 01-02-2021

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Conflict of Interest:
The authors declare that they have no conflict of interest.

Source of Funding: None

How to cite this article:
Kumar A, Chohan HT, Riasat MI, Sultan SF, Siddiqui SZ. Comparison of pre-emptive usage of ketamine and combination of ketamine with midazolam to prevent shivering during neuraxial block. J Surg Pakistan. 2020;25 (4):158-62. Doi:10.21699/jsp.25.4.6.