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A COMPARATIVE STUDY OF KETAMINE, MIDAZOLAM AND KETAMINE PLUS MIDAZOLAM FOR PREVENTION OF SHIVERING DURING SPINAL ANAESTHESIA

Anaesthesiology

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ABSTRACT

INTRODUCTION:- Spinal anaesthesia is one of the most popular and safe techniques used for various surgeries. A common problem that develops following spinal anaesthesia is shivering. Shivering is a physiologically stressful and undesirable outcome for a patient although its main role is to provide heat. It may occur in patients receiving regional anaesthesia or general anaesthesia. Shivering is preceded by core hypothermia and vasoconstriction above the level of block. Ketamine has been found to be effective for prevention and treatment of shivering. 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 anaesthesia. So, in the quest for safer and efficacious choice of drug, **our study plans to** compare 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 anaesthesia.

MATERIAL AND METHODS:- This study was conducted at Govt Medical College and Associate group of Hospitals, Kota from jan.2016 to dec.2016. We conducted a double blind, prospective, randomized controlled study of 120 cases from Orthopaedic department between age group 30-60 yrs of both sex. **We divided the cases into 4 groups of 30 each, as**

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

Standard protocol followed to administering regional anaesthesia. Axillary and tympanic temperature readings were taken using a standard procedure. Shivering was graded using a scale similar to that validated by **Tsai and Chu**. All data were collected and analysed with the help of suitable statistical parameters.

RESULTS:- Our study results in that the use of ketamine alone is definitely superior to placebo for the prevention of shivering after spinal anaesthesia. However the combination of ketamine plus midazolam is significantly superior to ketamine alone.

KEYWORDS

Spinal Anaesthesia, Ketamine, Midazolam, Placebo

INTRODUCTION

Spinal anaesthesia is one of the most popular and safe techniques used for various surgeries. A common problem that develops following spinal anaesthesia is shivering. This problem is seen in upto 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 anaesthesia is not completely understood. It may occur in patients receiving regional anaesthesia or general anaesthesia.[1] Shivering can cause several undesirable physiologic consequences, which include increase in oxygen consumption, carbon dioxide production 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 oxygen saturation (SpO_2) due to artifacts. 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 anaesthesia decreases the vasoconstriction and shivering thresholds. There is redistribution of heat from core to periphery due to spinal induced vasodilation. Shivering is preceded by core hypothermia and vasoconstriction above the level of block.[4,5] The core hypothermia following spinal anaesthesia 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] There are pharmacological ways for the prevention of shivering during the spinal anaesthesia. Several opioid and non-opioid agents have been used to prevent and treat shivering, However they do have adverse effects such as hemodynamic instability, respiratory depression and nausea and vomiting. Varieties of physical agents (radiant heat, special blankets) were also used to prevent shivering, but these measures were found to be burdensome and of limited success.[2]

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. **Sagir and colleagues** showed that the prophylactic use of 0.5 mg/ kg i.v. ketamine was effective in preventing shivering developed during regional anaesthesia, but patients may develop hallucinations and postoperative nausea or vomiting.[9] Among benzodiazepines, diazepam has been found to be effective in the prevention of postoperative shivering.[10] Midazolam is another benzodiazepine, which may decrease the incidence of shivering. 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 anaesthesia. So, in the quest for safer and efficacious choice of drug, **our study aims to** compare 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 anaesthesia.

MATERIAL AND METHOD

Study place and time:-

This study was conducted at Govt Medical College and Associate group of Hospitals, Kota from jan.2016 to dec.2016.

Study population:-

Patients admitted in Orthopaedic ward were the source of data. Patients undergoing elective surgery under regional anaesthesia were included in the study.

Methodology:-

We conducted a double blind, prospective, randomized controlled study of 120 cases from Orthopaedic department between age group 30-60 yrs of both sex . After obtaining approval from institutional ethics committee and written informed consent from the patients. We evaluated these patients pre-operatively for their fitness, for the

proposed surgical procedure under spinal anaesthesia. They were kept fasting for 10 to 12 hrs. **We divided the cases into 4 groups of 30 each, as**

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

The drug/placebo were 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. Standard protocol followed to administering regional anaesthesia. Patients were not given any pre-medication. Heart rate, blood-pressure and peripheral oxygen saturation were recorded using standard non-invasive monitors before intra-thecal injection and thereafter at 5, 10, 15, 20, 25 and 30 minutes. Before intra-thecal injection and at 10-minute intervals during the peri-operative period, body temperature (axillary and tympanic) was recorded. Axillary and tympanic temperature readings were taken using a standard procedure.. The ambient temperature was measured by a wall thermometer and maintained at 24 degrees Celsius.

Spinal anaesthesia was given at either L3/4 or L4/5 interspace with hyperbaric Bupivacaine (5 mg/ml) 15 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-thecal injection by an anesthesiologist who was blinded to the group allocation. 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**[11]

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 minute intervals. 15 minutes after spinal anaesthesia and concomitant administration of one of the prophylactic study drugs, if Grade 3 or 4 shivering was noted, the prophylaxis was regarded as ineffective, and i.v. Tramadol 1mg/kg was given**.**

Statistical analysis:-
The results of continuous variables are expressed as mean ± SD The difference between groups was assessed by suitable statistical tools. For all the tests a 'p' value of 0.05 and less was considered for statistical significance.

RESULTS :-

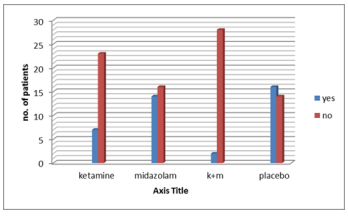

Figure 1 : Incidence of shivering at 15 minutes in the patients
The incidence of shivering is significantly lower in the ketamine and midazolam group. (P<0.05)

Table 1 : Axillary temperature at 10 minutes

Parameter	Ketamine (K)	Midazolam (M)	Ketamine + midazolam (KM)	Placebo (P)	Statistical test
Axillary temperature at 10 minutes	36.65±0.22	36.24 ±0.16	37.0 ± 0.13	36.4±0.17	Kruskal Wallis test with post hoc Dunn test

On comparing the axillary temperature at 10 minutes between the 4 groups using **Kruskal Wallis test with post hoc Dunn test**, it was observed that the axillary temperature at 10 minutes in the midazolam group is significantly lower than the ketamine group($p<0.001$), the temperature in the placebo group is significantly lower than the ketamine group, in the midazolam group is significantly lower than the ketamine and midazolam group ($p<0.001$) & the temperature in the placebo group is significantly lower than the ketamine and midazolam group ($p< 0.001$) .

Table 2 : Tympanic temperature at 10 minutes in the patients

Parameter	Ketamine (K)	Midazolam (M)	Ketamine + midazolam (KM)	Placebo (P)	Statistical test
Tympanic temperature at 10 minutes	36.95 ± 0.29	35.76 ± 0.11	36.69± 0.10	35.96± 0.16	Kruskal Wallis test with post hoc Dunn test

On comparing the tympanic temperature at 10 minutes between the 4 groups using Kruskal Wallis test with post hoc Dunn test, the temperature in the midazolam group is significantly lower than the ketamine group($p<0.001$), the temperature in the placebo group is significantly lower than the ketamine group($p<0.001$), the temperature in the midazolam group is significantly lower than the ketamine and midazolam group.($p<<0.001$). The temperature in the placebo group is significantly lower than 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 30-40% 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] . It can aggravate wound pain by stretching the incisions and increase intra-cranial and intra-ocular pressure. It can increase O_2 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]

The physiological definition of hypothermia is commonly accepted to be core hypothermia greater than one standard deviation (SD) below the mean core temperature for that mammal in a thermo-neutral environment, under resting conditions. The core body temperature decreases as a result of the sympathetic block, peripheral vasodilatation and increased cutaneous blood flow, leading to increased heat loss through the skin. This is further aggravated by cold temperature of the operation theatre, rapid infusion of cold intravenous fluids and cold anaesthetic drugs on the thermal sensitive receptors of the spinal cord.[13]

A motor centre for shivering, where the impulses from cold receptors impinge, exists adjacent to the centre in the posterior hypothalamus. Impulses from the pre-optic heat sensitive area in the anterior hypothalamus normally inhibit this centre, but when the cold impulses exceed the rate at which the former may be received, this motor centre for shivering becomes activated by a 'spill-over' of signals , resulting in impulses sent bilaterally into the anterior motor neurons of the spinal cord. This causes an initial increase in the tone of skeletal muscles throughout the body, but when this muscle tone exceeds a certain limit, shivering is observed. This is achieved by increasing the sensitivity of the muscle stretch reflex.[4].

Thus, 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]

According to **Buggy and Crossley** thermoregulatory impairment is caused by general as well as regional anaesthesia. This is characterized by an increase in warm-response thresholds and decrease in cold-response thresholds such that the normal inter-threshold range is

increased from 0.4 to 4° C. This impairment is different according to the use of different drugs.

Intra-operative use of pethidine has been found to completely abolish shivering during the post-anaesthetic period, in majority of the patients. Use of propofol has been found to reduce the incidence of post-anaesthetic shivering when compared to thiopental. It has been found that anaesthetic pre-medication with muscarinic antagonists like atropine or glycopyrrolate predisposes to post-anaesthetic shivering.[4]

Core hypothermia during prolonged epidural anaesthesia however, is less than after general anaesthesia due to vasoconstriction above the level of the block. Accelerated heat loss during regional epidural anaesthesia is caused by reduced vasoconstriction threshold in association with vasodilation in the part of the body below the block. When given in combination with general anaesthesia, the vasoconstriction threshold is reduced more, along with increasing the rate of core cooling. Furthermore, awareness of core hypothermia is impaired during epidural anaesthesia.[4] Many other causes like sympathetic over-activity and pyrogen release may also be responsible for shivering.[12]

Hence, this study was undertaken to compare ketamine, midazolam, ketamine plus midazolam and placebo for the prevention of shivering in patients undergoing elective surgery under spinal anesthesia.

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. NMDA antagonists have been found to modulate thermoregulation at various levels. NMDA modulates the noradrenergic and serotonergic neurons in the locus coeruleus. Serotonin enhances the effect of NMDA receptors in the dorsal raphe nucleus. NMDA receptors also modulate the ascending nociceptive transmission in the spinal cord. In addition ketamine also has other properties like κ opioid agonism, amine uptake blockade in the descending inhibitory monoaminergic pain pathways, local anaesthetic action and interaction with muscarinic receptors.[51] The post-operative shivering inhibition activity of ketamine was found to be more rapid than meperidine in the studies by **Kose et al[14] and Gecaj-Gashi A et al[15].** However the potential for side effects with ketamine being more than that with meperidine, its usefulness would be limited in the prevention of post-operative shivering. Ketamine produces vivid dreams, extra-corporeal experiences, hallucinations and illusions. These may be overcome with the use of low dose of ketamine.[13]

Some studies by **Kurz et al[16] and Grover et al[17]**, reported little or no effect of midazolam in prevention of post-operative shivering. **Grover et al** found that midazolam is ineffective in preventing shivering at the end of the anaesthetic procedure**.[17]** In our study,shivering was graded using a scale similar to that validated by **Tsai and Chu**.[11] 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-P group 53.3%. This mirrors the findings of Honoramand 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.[18] These patients were treated with Inj.Tramadol 1 mg/kg and shivering ceased in all patients. None of the patients in the KM group exhibited Grade 3 or 4 shivering.

OUR RESULTS SHOW THAT KETAMINE IS SUPERIOR TO PLACEBO OR MIDAZOLAM FOR PREVENTION OF SHIVERING, BUT THE COMBINATION OF KETAMINE PLUS MIDAZOLAM IS DEFINITELY A BETTER OPTION.

Axillary temperature:-

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 Honoramand 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). Using ANOVA followed by Bonferroni's post hoc testing, it was found that the axillary body temperatures in the group ketamine plus midazolam were significantly higher than in the other groups in the 10th to 80th minute(P<0.044)[18]

Tympanic temperature:-

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 our study, we used tympanic temperature to gauge core temperature, while a similar study by Honoramand et al ,used nasopharyngeal temperature. This was done keeping in mind the discomfort a nasopharyngeal temperature probe would cause to an un-sedated patient. However, the levels of agreement are comparable between the nasopharyngeal and tympanic sites.[19]

CONCLUSION: -

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

CONFLICT OF INTEREST:-

there is no conflict of interest between authors.

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