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EFFICACY OF KETAMINE-MIDAZOLAM COMBINATION IN PREVENTION OF SHIVERING DURING SPINAL ANAESTHESIA- A COMPARATIVE STUDY

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ABSTRACT Shivering is a frequently noted side effect of spinal anaesthesia. We conducted a prospective randomized study involving 210 patients posted for elective lower limb surgery under subarachnoid block. Patients in group A received ketamine 0.25 mg/kg with midazolam 0.02mg/kg, group B patients received ketamine 0.25 mg/kg with midazolam 0.04 mg/kg and patients in group C received normal saline. The incidence of shivering in group C was 67% which was statistically significant while it was 2.85% in group A and 0.7% in group B. By the end of two hours the shivering incidence was 17%, 21.4% and 11.4% in group A, group B and group C respectively. Maximum mean sedation score was noted in group B which was statistically significant. Ketamine-midazolam combination administered prophylactically results in significant reduction of shivering but the effect is short lived. Higher dose of midazolam offers no advantage and results in excessive sedation.

KEYWORDS : ketamine, spinal anaesthesia, hypothermia, shivering

INTRODUCTION

The normal core body temperature in humans is 36.5-37.5^0 C and is maintained in this narrow range even in adverse conditions by various physiological and behavioural adaptations. Shivering is one such thermoregulatory response characterised by fasciculations involving various muscle groups and thereby augmenting metabolic heat production.

Spinal anaesthesia is associated with impairment of autonomic thermoregulation resulting in core hypothermia that triggers shivering. The incidence of shivering has been reported to be about 36% to 85% after spinal anaesthesia [1, 2]. Perioperative shivering, apart from the obvious discomfort, causes various detrimental effects that includes increased oxygen consumption and carbon di oxide production, surge in catecholamines, tachycardia, hypertension, raised intra ocular and intracranial pressures[3,4].

Shivering during spinal anaesthesia can be substantially reduced by maintaining strict normothermia but pharmacotherapy remains the mainstay for treating persistent shivering. Although ketamine, pethidine, alfentanil, tramadol, magnesium sulfate, ondansetron, dolasetron, and physostigmine have been used to treat or prevent shivering, the ideal drug has not yet been found[5] . We conducted a randomized control study to compare the efficacy of two different combinations of ketamine with midazolam and placebo (saline) administered prophylactically for the prevention of shivering in patients who underwent elective lower limb surgery under spinal anaesthesia.

MATERIALS AND METHODS

This study was conducted in the Department of Anesthesiology at a tertiary care teaching Hospital, Bengaluru over a period of 12 months from October 2013 to October 2014. Approval was obtained from the institutional ethical committee and informed written consent taken from the patients willing for participation in the study. A total of 210 patients of either sex aged between 18-60 years and belonging to ASA physical status I & II scheduled for elective surgery of lower limb under spinal anaesthesia were selected. This was a double blinded randomized, placebo control study done to compare and assess the effectiveness of two combinations of ketamine-midazolam in prevention of shivering, to compare the side effects of the 2 groups and find an optimum combination of the same. Patients with extensive fractures, massive wounds, burns, those who received massive blood transfusions, patients with history of thyroid disorders, psychiatric illness, alcohol or substance abuse, patients with initial hypothermia and febrile illness were exempted from the study.

Two hundred and ten patients were randomized using computer generated random number tables into three groups with 70 in each group. Group A patients received a combination of midazolam 0.02mg/kg and ketamine 0.25 mg/kg; Group B patients received midazolam 0.04 mg/kg with ketamine 0.25 mg/kg while patients in Group C received normal saline.

All patients were administered oral Alprazolam 0.5mg and Ranitidine 150 mg the night before surgery. Patients were kept nil per oral for 8 hours prior to surgery as per institutional norms. After receiving the patients in the operating room IV line was secured and fluids started, monitors were connected to patients that included ECG, pulse oximetry, non-invasive blood pressure and axillary skin temperature. Subarachnoid block (SAB) was achieved with 3ml of 0.5% hyperbaric bupivacaine injected intrathecally at L2/3 or L3/4 interspace with patient in lying position. The study drug (diluted in a 2ml syringe and coded) was administered by the attending anaesthetist who was blinded to the study after performing the SAB. All patients were placed in supine position with their upper torso and arms covered with a blanket and operating room temperature was maintained at 24^{0}C throughout the surgery. No convection warmers or fluid warmers were used during the procedure

The incidence and severity of shivering as observed in the upper torso and upper limbs was recorded and graded using Tsi and Chu scale which is as follows: Class 0: Shivering absent; Class 1: Piloerection/peripheral vasoconstriction present but no visible shivering; Class 2: Muscular activity confined to single group of muscle; Class 3: Muscular activity involving more than one muscle group but not generalized; Class 4: Generalised shivering involving the whole body[6]. Heart rate, mean arterial pressure, oxygen saturation and axillary temperatures were recorded during surgery at 5, 10, 20, 30 min, after which the parameters were measured every 15 minutes for a total duration of 2hrs. All patients received oxygen supplementation via facemask at 4L/min. If the patient continued to shiver after 30 minutes with a grade 2 or more then IV Pethidine 25mg bolus was used as a rescue drug. Any side effects such as sedation, nausea, vomiting, sweating, nystagmus and hallucinations were noted. Degree of sedation was assessed using the following scale- Grade 1: Fully awake and oriented; Grade 2: Drowsy; Grade 3: Eyes closed but arousable to command; Grade 4: Eyes closed but arousable to mild physical stimulation; Grade 5: Eyes closed but unarousable to mild physical stimulation[7].

Statistical analysis

Sample size was calculated based on a study by Misiran K and Aziz FZ which showed the incidence of shivering at 46% in control group and 16% in the ketamine-midazolam group[8]. Assuming this difference to

be significant, a sample size of 70 patients per group was calculated with a power of 80% and Alpha error of 5%. Data was analysed using SPSS 22 version software. Chi-square was used as test of significance for categorical data. For parametric data ANOVA (Analysis of Variance) was used as test of significance to identify the mean difference between three groups (A, B and C). Kruskal Wallis test was used for comparison of Sedation and Shivering score over time; p value <0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

Two hundred and ten patients were included in the study. Patient demographics including age, sex, ASA status baseline temperature and duration of surgery were comparable in all the three groups. The incidence of shivering (grade ≥2) in group C was found to be 67% (47/70) and was maximum during the 20-30 minutes interval as compared to group A and group B where the incidence was low at 2.85% and 0.7% respectively during the same time interval which was statistically significant (p<0.001). At the end of 1hour the incidence of shivering in group C had reduced to 31.4% while it remained almost unchanged in the other two groups (group A-2.85% and group B- 0). Use of pethidine could have reduced the incidence of shivering in group C.By the end of two hours the shivering incidence was 17%, 21.4% and 11.4% in group A, group B and group C respectively (Figure 1and 2). Recurrence of shivering was observed in 17.1% of Group A subjects and 21.4% of Group B subjects which was statistically not significant (p= 0.52). Rescue drug i.e. Pethidine was administered in 11.4% of Group A subjects and 14.3% of Group B subjects which was statistically insignificant (p= 0.61).

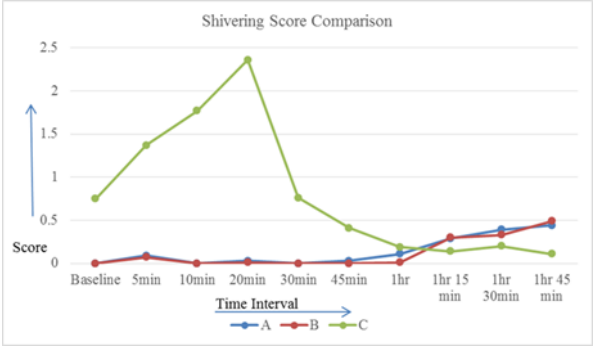

Figure 1: Comparison of shivering scores among three groups

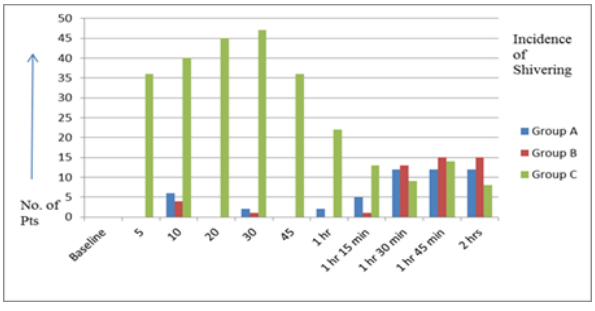

Figure 2: Incidence of shivering among three groups

Patients in all the three groups showed a drop in axillary temperature within the first 30 minutes of surgery, compared to the baseline values (p-value ≤0.001). However, there was no significant difference between the three groups. The heart rate in group A and B did not change much over the time and it remained close to its baseline value but patients in group C showed significant increase in heart rate that was observed at all the intervals post anaesthesia. When mean arterial pressure (MAP) was compared with baseline at different time intervals after anaesthesia patients in group A showed significant increase in MAP from baseline value at all intervals in the first hour but later there was no significant variation. In contrast to this patients in group B and group C showed no significant variation in MAP from baseline at all the intervals.

There was no difference in sedation score between group A and group B initially but after administration of the drugs, significant difference (p< 0.001) in sedation score was noted between these two groups at all intervals. The maximum mean sedation score recorded in group A was 2.6 at 20 minute interval while in group B it was 4.25 noted at 10 minute interval (Figure 3). Hallucination was experienced in only 1 patient in group A, none in the other groups. Nystagmus was observed in 11 patients in group A and 8 in group B which was not statistically significant (p>0.05).

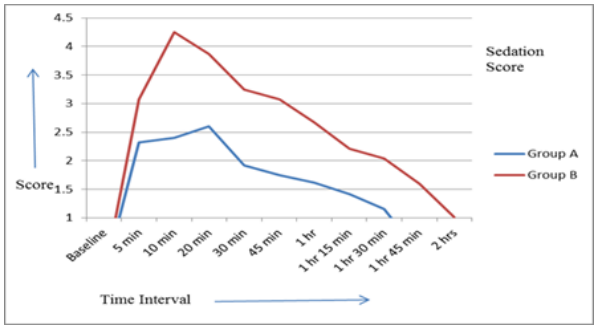

Figure 3: Comparison of sedation scores between group A and B

Shivering is an unpleasant and adverse side effect of neuraxial anaesthesia. The incidence of shivering associated with neuraxial anaesthesia was 55%, based on the meta-analysis by Crowley and Buggy[9]. Shivering during spinal anaesthesia can be addressed by taking measures to prevent heat loss and maintaining normothermia. However, in spite of this low-intensity, shivering-like tremors can occur in normothermic patients which is not thermoregulatory. A study by Butwick et al concluded that intraoperative forced air warming did not prevent perioperative hypothermia, when compared to the control group who did not have forced air warming. They also found that the incidence and intensity of shivering episodes were not significantly different between the two groups[10].

Sedatives are frequently administered during neuraxial anaesthesia. With the exception of midazolam, all of them significantly impair thermoregulatory control[11]. Various drugs have been tried to treat and prevent shivering during spinal anaesthesia; ketamine and midazolam combination is one among them. Honarmand and Safavi studied the effect of ketamine, midazolam, combination of ketamine plus midazolam and placebo in preventing of shivering during spinal anaesthesia and found that the incidence of shivering was high in the placebo group at 60% while it was significantly low (3.3%) in ketamine- midazolam group. These results are in agreement with our study; the incidence of shivering in the control group was found to be 67% and was maximum during the 20 to 30 minutes interval. Where as in patients who received ketamine and midazolam, shivering was observed in only 2.85%[12].

Misiran K and Aziz FZ studied the effect of midazolam plus ketamine in the prevention of shivering during spinal anaesthesia for emergency lower limb surgery[8] which reported a lower incidence of shivering (46%) in the control group as compared to ours, this could be explained by the use of warm fluids and air-warming devices for all their patients in the intraoperative period and moreover the observation period was limited to the first 30 minutes after spinal anaesthesia to exclude other confounding factors. The incidence of shivering in ketamine-midazolam group however was comparable with our results.

The decreases in axillary temperature was noted in all the groups within the first 30 minutes which was statistically significant when compared with the baseline level (P < 0.05), a finding similarly seen in earlier studies. Hypothermia is common during regional anaesthesia where core temperature typically decreases 0.5^0C to 1.0^0C. This drop in core temperature results from an internal core-to-peripheral redistribution of body heat and increased cutaneous heat loss from the vasodilated blocked segments[13]. Apart from this spinal anaesthesia also decreases the threshold triggering vasoconstriction and shivering (above the level of block) by 0.6^0C[14].

The maximum mean sedation score of 4.25 was noted in group B, this could be due to a higher dose of midazolam (0.04) used in this group. In group A the maximum mean sedation score was 2.6, most patients in group C had a sedation score of 1. These results are similar to the study by Misiran K and Aziz FZ where a high mean sedation score (3) was observed in the group which had a higher dose of midazolam[8] (0.04mg/kg) Side effects such as nystagmus and hallucinations were noted in the ketamine-midazolam group but was not severe as we used

a small dose of ketamine combined with a benzodiazepine.

Ketamine belongs to phencyclidine group of drugs, it acts as an antagonist at N-methyl-D-aspartic acid (NMDA) receptors. Apart from its anaesthetic and analgesic properties ketamine is known to be involved in the modulation of thermoregulation at various levels. Ketamine probably controls shivering by non-shivering thermogenesis, either by action on the hypothalamus, or by the β-adrenergic effect of norepinephrine. The NMDA receptor acts by modulating the noradrenergic and serotoninergic neurons in the locus ceroleus. NMDA receptors also modulate ascending nociceptive transmission at the dorsal horn of the spinal cord[15].

Midazolam is a short-acting benzodiazepine that acts at GABA receptors and is normally used as an anxiolytic and to supplement sedation during spinal anaesthesia. Animal studies have shown that benzodiazepines reduce repetitive firing in response to depolarizing pulses in spinal cord neurons via GABA receptors[16]. Such inhibitory functions may be responsible for blocking the conduction of afferent impulses from muscle spindles and cutaneous receptors for cold to the higher centres, thereby suppressing shivering. Midazolam also reduces side effects of ketamine like hallucinations and delirium.

Ketamine and midazolam combination was effective in prevention of shivering as shown by our results but at the end of two hours more patients started to shiver in group A and group B as compared to group C. This could be due to short lasting effect of the drugs used in these groups. In the study by Misiran K and Aziz FZ observation was limited for the initial 30 minutes to avoid the confounding factors that might come into play in the later period.

CONCLUSION

Combination of ketamine and midazolam administered prophylactically during spinal anaesthesia results in significant reduction of shivering, but this benefit lasted for about an hour as patients had recurrence of shivering after this period. It was also seen that a higher dose of midazolam offered no advantage over the lower dose, but only increased the risk of excessive sedation. Low dose midazolam with ketamine could be used as an alternative to prevent shivering during spinal anaesthesia for short procedures.

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