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KETAMINE, CLONIDINE AND TRAMADOL FOR CONTROL OF SHIVERING UNDER NEURAXIAL ANESTHESIA

Dr. Ketki Jandial*

(MD Anesthesia) Super Specialty Hospital, Jammu, J&K: 180001.

***Corresponding Author: Dr. Ketki Jandial**

(MD Anesthesia) Super Specialty Hospital, Jammu, J&K: 180001.

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ABSTRACT

Background: Shivering tends to increase expenditure of cardiac and systemic energy, and interferes with pulse rate, blood pressure (BP) and electrocardiographic (ECG) monitoring. It also interferes with haemodynamic monitoring intraoperatively. Shivering per se may aggravate post-operative pain, simply by stretching of surgical incision. Therefore, the present study was done to assess the efficacy of ketamine, clonidine and tramadol when used prophylactically to control shivering under neuraxial blockade. **Methods:** A double blind randomized clinical trial study was performed in the Department of Anesthesia, GMC Jammu, on 144 patients of ASA grade 1 and 2, belonging to either gender or age between 18 to 65 years, after taking written- informed consent. Patients, undergoing lower abdominal or lower limb surgery were included in the study. **Results:** Ketamine had significant role in sedation degrees as compared to other groups and maintained cardio-respiratory stability and prevented recall of un-pleasant events in the surgery. There was a greater fall in core body temperatures in the placebo group as compared with the ketamine, tramadol and clonidine groups in our study. The incidence of shivering was 23/32 (71.8%) in the placebo group. **Conclusion:** Ketamine 0.5 mg/kg, clonidine 75 mcg or tramadol 0.5 mg/kg i.v. prophylactically just before neuraxial blockade significantly decreased the incidence of shivering without causing any major side-effects. Using ketamine may be more beneficial as it improves the hemodynamic profile and sedates the patient effectively, which increases patient comfort during surgery, maintains cardiorespiratory stability and prevents recall of unpleasant events during the surgery.

KEYWORDS: Shivering, Ketamine, Clonidine, Tramadol, Neuraxial Blockade.

INTRODUCTION

In patients undergoing neuraxial or regional anesthesia, heat loss and core to peripheral redistribution of body heat causes the core temperature to decrease and shiveringoccurs to prevent further hypothermia.[1,2] Therefore, the main causes for shivering intra-operatively or post-operatively are: temperature loss, decreased sympathetic tone and systemic release of pyrogens.[3] It is a potentially serious complication, resulting in increased metabolic rate, increased oxygen consumption (up to 100-600) along the raised carbon dioxide (CO_2) production, lactic acidosis, increased intraocular and intracranial pressureand increased cardiac output. Shivering tends to increase expenditure of cardiac and systemic energy,[4] and interferes with pulse rate, blood pressure (BP) and electrocardiographic (ECG) monitoring.[5,6] It also interferes with haemodynamic monitoring intraoperatively. Intra- and post-operative management of shivering are usually done by external heating (forced air warming, warming blankets, warmed fluids) or pharmacological interventions. Various drugs from different groups like opioids, 5-hydroxytryptamine receptor (5-HT3) antagonists, N-methyl D-aspartate (NMDA) receptor antagonists, cholinomimetics and biogenic amines have been used to tackle the problem.[7,8] Due to shivering and thermal discomfort. the quality of patient's recovery suffers. Moreover, shivering per se may aggravate post-operative pain, simply by stretching of surgical incision. Hence pharmacological methods using different drugs, which have prophylactic anti-shivering properties, are used. Shivering under neuraxial anaesthesia is a common problem faced by anaesthetists; therefore, a randomized double-blind study was conducted using commonly available drugs like ketamine, clonidine and tramadol to assess their efficacy when used prophylactically to control shivering under neuraxial blockade.

MATERIAL AND METHODS

A randomized clinical trial study was performed in the Department of Anesthesia, GMC Jammu, on 144 patients of ASA grade 1 and 2, belonging to either gender or age between 18 to 65 years, after taking written- informed consent.

Inclusion Criteria: Patients, undergoing lower abdominal or lower limb surgery were included in the study.

Exclusion Criteria: Patients suffering from

neuromuscular disease, hyperthyroidism, history of cardiopulmonary disease, psychological disease, refusal to participate or temperature >38°C or <36.5°C.

Following a detailed pre-anaesthetic checkup along with relevant investigations, patients were brought to the operation theatre (OT) and relevant monitoring attached. All the patients were pre-loaded with Ringer lactate 10 mL/kg before giving neuraxial blockade. The study drug was coded and presented to the anaesthetist not involved in the management of the patient and administered by intravenous (i.v) route just before giving the block. The study drug and saline were pre-heated to 37°C before administering them to the patient. The patients were randomized into four groups of 50 patients each as follows.

Group P: Patients received 10 mL normal saline
Group K: Patients received ketamine 0.5 mg/kg i.v. diluted to 10 mL in saline
Group C: Patients received clonidine 75 mcg i.v. diluted to 10 mL in saline
Group T: Patients received tramadol 0.5 mg/kg i.v. diluted to 10 mL in saline.

The IV fluids used were pre-heated to 37°C before using them for the patients. The temperature of the OT was maintained at 24±1°C for all the patients. Neuraxial anaesthesia was instituted at either L3-4 or L4-5 interspaces using 2.8 mL (14 mg) of hyperbaric bupivacaine 0.5% (with 8.5% dextrose) using a 25 gauge quincke's spinal needle. During the intraoperative period, after noting the baseline parameters, pulse rate, non-invasive blood pressure (NIBP), oxygen saturation, temperature (core and surface) and level of sensory block were assessed at 5-min intervals. Sensory block was assessed every 5 min till there was no change in the level of anesthesia, and every 15 min thereafter. The core temperature was measured by a nasopharyngeal thermometer and surface temperature by an axillary thermometer. The prophylaxis was regarded as ineffective if the patients exhibited grade 3 shivering any time during the study and then IV pethidine 25 mg was administered as a rescue drug.

Hallucination as a side- effect was defined as a false sensory experience where the patients reported that they saw, heard, smelled, tasted or felt something that was non- existent. The attending anaesthetist also assessed the degree of sedation on a 5-point scale.[9] 1= fully awake and oriented, 2= drowsy, 3= eyes closed but arousable to command, 4= eyes closed but arousable to mild physical stimulation and 5= eyes closed but unarousable to mild physical stimulation.

Shivering was graded using a scale validated by Tsai and Chu[10]: grade 0=no shivering, 1=piloerection but no visible shivering, 2=muscular activity in only one group of muscles, 3=muscular activity in more than one muscle group but not generalized and 4=shivering involving the whole body. During surgery, the shivering scale was recorded at 5-min intervals up to 90 min of surgery.

Side-effects such as hypotension, nausea, vomiting, hallucinations and sedation were also recorded. Hypotension was defined as a decrease in mean blood pressure (MBP) of more than 20% from the baseline. Hypotension was treated with I.V. incremental bolus dose of mephentermine 3 mg and a further I.V. infusion of Ringer lactate. If patients developed nausea and vomiting, I.V. metoclopramide was administered. Approval by the Institutional Ethical Committee was duly taken. All parameters were analyzed using MS Excel 2010 software. The data among groups were compared using one-way ANOVA. The withingroup data were analyzed using repeated-measure analysis of variance. The incidence of shivering and side-effects were compared using the chi-square test. The data was expressed as mean ± SD. A value of $p<0.05$ was considered as statistically significant.

RESULTS

Table 1: Different grades of shivering in all three groups.

Shivering grade	Group P 36 (Placebo)	Group A 36 (Ketamine)	Group B 36 (clonidine)	Group C 36 (Tramodol)	P value
Grade-0	13	28	33	31	<0.01*
Grade-I	06	02	01	01	
Grade-II	06	02	01	01	
Grade-III	11	04	01	03	
Grade-IV	0	0	0	0	

Degree of freedom-0.11, P<0.05 = significant

Table 2: Sedation Score in different groups.

Sedation Score	Group P (36)	Group A (36)	Group B (36)	Group C (36)	P value
Grade-I	12	06	16	19	0.27
Grade-II	10	11	11	12	
Grade-III	12	17	07	04	
Grade-IV	02	02	02	01	

P<0.05 = significant

DISCUSSION

Ketamine is a competitive receptor antagonist of NMDA, which increases blood pressure, heart rate and cardiac output because of direct sympathetic stimulation and inhibition of norepinephrine uptake into the post-ganglionic sympathetic nerve endings, and may decrease core to peripheral redistribution of heat. However, it may cause side-effects such as hallucination.[11]

Tramadol is a centrally acting analgesic that has weak opioid agonist properties. It also inhibits serotonin and norepinephrine uptake in the spinal cord and is effective in the treatment of post-operative shivering after regional and general anesthesia. Tramadol may cause nausea and vomiting too, but has a low risk of respiratory depression, tolerance and dependence.[12]

Clonidine's anti-shivering effect can be found at three levels. It decreases the thermoregulatory threshold for vasoconstriction and shivering as the hypothalamus contains high-density receptors. It also reduces spontaneous firing in locus coeruleus – a pre-shivering centre in the pons. The depressor effects of these neurotransmitters at the dorsal horn modulate cutaneous thermal inputs in addition to noxious and mechanoreceptive transmission.[13] Side effects of Clonidine are hypotension and bradycardia.

The present study has shown that prophylactic use of ketamine, clonidine and tramadol were effective in preventing shivering during neuraxial anaesthesia without causing any untoward side-effects, but different grades of shivering in all three groups. The incidence of shivering was 23/32 (71.8%) in the placebo group, which was comparable to those reported by Wason et al.[14] However, some studies have reported a lower incidence of shivering at 40% only. Moreover, the spinal anaesthesia causes a two- to three-level higher level of autonomic blockade than the sensory level achieved, as compared with extradural, in which autonomic blockade is the same or one level higher than the sensory level achieved.

The demographic profile of hemodynamic parameters (heart rate and mean blood pressure) was compared in all three groups.

Sagir et al.[15] and Dal et al.[16] also found ketamine 0.5 mg/kg i.v. to be effective in controlling shivering under neuraxial blockade. Bilotta[14] and Chan et al.[17] found tramadol to be a promising drug in doses of 0.5 mg/kg and 0.25 mg/kg I.V., respectively, in controlling shivering under neuraxial blockade.

There was a greater fall in core body temperatures in the placebo group as compared with the ketamine, tramadol and clonidine groups in our study. This trend in core temperature is similar with the trends reported by Sagir[15] and Tewari et al.[18] Greater fall in core temperature in the placebo group as compared with the other groups may be because of the study drug effect.

In our study, the incidence of side-effects was not significantly different among the groups. Tramadol has the potential to cause nausea and vomiting, but the incidence of nausea and vomiting in the study groups was comparable with the placebo group.[19]

Clonidine is highly lipid soluble and easily crosses the blood brain barrier. Tramodol is an opiod analgesic with opoid action preferably mediated via μ(mu) receptors with minimal effect on kappa and delta binding sites. Tramadol also activates mononergic receptors of the descending neuraxial inhibiting pain pathway. The anti-shivering action of tramadol is probably mediated via its opiod or serotogenergic and noradrenergic activity or both. Ketamine is a competitive receptor antagonist NMDA (N-methyl-D aspirate) which has role in thermo regulation at various levels. It increases blood pressures, heart-rate and cardiac output because of direct sympathetic stimulation and inhibition of norephinephrine up take into post- ganglion sympathetic nerve endings and may decrease core to peripheral redistribution of heat.[20]

Ketamine causes significant grades 3 and 4 sedation as compared with placebo, clonidine and tramadol. Clonidine also has the potential to cause sedation, but, in our study, clonidine did not cause any significant sedation as compared with placebo. In the present study ketamine had significant role in sedation degrees as compared to other groups and maintained cardio-respiratory stability and prevented recall of un-pleasant events in the surgery. This may be beneficial as it increases patient comfort, maintains cardiorespiratory stability, improves surgical conditions and prevents recall of unpleasant events during the surgery.[21]

CONCLUSION

Ketamine 0.5 mg/kg, clonidine 75 mcg or tramadol 0.5 mg/kg I.V. prophylactically just before neuraxial blockade significantly decreased the incidence of shivering without causing any major side-effects. Moreover, Ketamine had maintained hemodynamic stability and prolong sedation as compared to other 2 groups. Thus, using ketamine may be more beneficial as it improves the hemodynamic profile and sedates the patient effectively, which increases patient comfort during surgery, maintains cardiorespiratory stability and prevents recall of unpleasant events during the surgery. But this prophylactic study demands further genetic, nutritional, patho-physiological, neurotransmitters, pharmacological study to understand the exact mechanism.

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