A PROSPECTIVE RANDOMIZED STUDY OF COMPARISON OF PROPHYLACTIC KETAMINE, CLONIDINE AND TRAMADOL FOR THE CONTROL OF SHIVERING UNDER NEURAXIAL ANAESTHESIA

Anaesthesiology

Dr. Rajeev Krishan	MBBS, M.D. (Anaes.), Senior Resident, Department of Anaesthesia, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar.
Dr. Praveen Kumar Singh*	MBBS, M.D. (Anaes.), Senior Resident, Department of Anaesthesia, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar. *CorreSponding Author
Dr. Chandeshwar Choudhary	MBBS, M.D. (Anaes.), Associate Professor, Department of Anaesthesia, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar.
Dr. Debarshi Jana	Young Scientist (DST), Institute of Post-Graduate Medical Education and Research, A.J.C. Bose Road, Kolkata-700020, West Bengal, India.

ABSTRACT

Background: Thermoregulatory system coordinates defenses against environmental temperature to maintain internal core temperature within a narrow range, thus optimizing normal body function and homeostasis in humans. Anaesthetic induced thermoregulatory impairment and hence hypothermia in cold environments. Shivering is an important complication of hypothermia. Shivering is an involuntary, oscillatory muscular activity that augments metabolic heat production upto 600% above basal level to increase temperature. It is associated with substantial adrenergic activation, discomfort and can double or even triple oxygen consumption and carbon dioxide production. Potent anti-shivering properties have been attributed to numerous drugs including biogenic monoamines, cholinomimetics, cations, endogenous peptides and possibly N-methyl-D-aspartate (NMDA) receptor antagonists like ketamine, tramadol and clonidine.

Aim: To evaluate the effectiveness of prophylactic use of intravenous ketamine, clonidine and tramadol in control of shivering and to note any side-effects of the drugs used.

Methods: A total number of 120 ASA I and 2 patients of either sex belonging to age group 18-60 years posted for Lower Abdomen and Lower Limb surgeries under subarachnoid block were divided into four groups of 30 each. Group P (control group): Patients received 10mL of normal saline IV as placebo. Group K: Patients received Inj. Ketamine 0.5mg/kg BW IV diluted to 10ml in Normal Saline. Group C: Patients received Inj. Clonidine 75mcg IV diluted to 10ml in Normal Saline. Group T: patients received Inj. Tramadol 0.5mg/kg BW IV diluted to 10ml in normal saline.

Results: We conclude that giving Ketamine 0.5mg/kg, Clonidine 75mcg or tramadol 0.5mg/kg i.v. prophylactically just before subarachnoid block significantly decreased the incidence of shivering without causing any major side effects.

Conclusion: Ketamine, Tramadol or Clonidine decrease shivering during spinal anesthesia.

KEYWORDS

INTRODUCTION

In homeothermic species, a thermoregulatory system coordinates defenses against environmental temperature to maintain internal core temperature within a narrow range, thus optimizing normal body function. The combination of anaesthetic induced thermoregulatory impairment and exposure to a cool environment makes most unwarmed surgical patients hypothermic, as Pickering wrote in 1956: "The most effective system for cooling a man is to subject him to anaesthesia". Except in some isolated cases temperature monitoring has not yet become a standard practice, nor are the measures instituted to lessen changes in core temperature during the perioperative period. Shivering is an important complication of hypothermia. Obvious etiology although is said to be cold induced, but some shivering like tremors are not thermoregulatory. Electrophysiological studies suggest that some anterior hypothalamic neurons act as "Sensors" as well as "integrators" in human brain Shivering is an involuntary, oscillatory muscular activity that augments metabolic heat production upto 600% above basal level¹. Initial hypothermia in regional anaesthesia results from redistribution of body heat from the core to the periphery. Shivering occurs in approximately 50% of patients with a core temperature of 35.5 degree centigrade and in 90% of patients with a core temperature of 34.5 degree centigrade.

Shivering is associated with substantial adrenergic activation and discomfort. It can double or even triple oxygen consumption and carbon dioxide production causing adverse myocardial outcomes. Mostly due to marked increase in plasma catecholamine. Shivering increases, lactic acidosis, intraocular pressures, intracranial pressures and interferes with haemodynamic monitoring. Hence temperature monitoring must be accurate and consistent. Various sites for monitoring Core temperature are pulmonary artery, distal esophagus, nasopharynx and tympanic membrane. Shivering should first of all be prevented, thereby offsetting hypothermia. If it does occur, it is treated, mainly by warming the patient and then administering medication to inhibit it.

Potent antishivering properties have been attributed to numerous drugs. Including pethidine, fentanyl, alfentanil, sufentanil, tramadol, buprenorphine, doxapram, clonidine & ketanserin etc. These drugs are substances of several classes including biogenic monoamines, cholinomimetics, cations, endogenous peptides and possibly N-methyl-D-aspartate (NMDA) receptor antagonists acting on central thermoregulatory control mechanisms. Tramadol inhibits reuptake of 5 HT, norepinephrine and dopamine and, facilitates 5 HT release. Also on cerebral alpha 2 adreno receptors. Ketamine, a competitive NMDA-receptor antagonist, also inhibits postanaesthetic shivering by acting on preoptic anterior hypothalamus and locus coeruleus. Cerebral alpha 2 adreno receptors agonist also play a role as by Clonidine.

MATERIAL AND METHODS

This prospective observational study was conducted in the department of anaesthesia in Sri Krishna Medical College and Hospital, Muzaffarpur, Bihar and informed written consent from all the patients for participation in this study.

A complete pre-anaesthetic evaluation was done at least 24hrs prior to surgery. A total number of 120 ASA I and 2 patients of either sex belonging to age group 18-60 years posted for Lower Abdomen and Lower Limb surgeries under spinal anesthesia were divided into four groups of 30 each.

EXCLUSION CRITERIA:

- Neuromuscular diseases,
- Hyperthyroidism,
- History of cardiopulmonary disease,
- Psychological disease,
- Refusal to participate or
- Temperature > 38°C or < 36.5°C

Preoperative:

All the patients were kept fasting 6 hrs prior to surgery. On the day of surgery baseline heart rate, non-invasive Blood pressure, respiratory

rate, oxygen saturation, electrocardiogram was recorded. Intravenous line was established by 18G size intravenous cannula. All the patients were given antiemetic palonosetron (0.1125mg), inj. Pantoprazole 40mg and lactated ringer solution 10ml/kg bodyweight within half an hour prior to subarachnoid block. The drug under observation was administered by intravenous (i.v) route just before giving the block. The observational drug, saline and I/V fluids will be pre heated to 37°C before administering them to the patients.

Group P (control group): Patients received 10mL of normal saline IV as placebo.

Group K: Patients received Inj. Ketamine 0.5mg/kgBW IV diluted to 10ml in Normal Saline.

Group C: Patients received Inj. Clonidine 75mcg IV diluted to 10ml in Normal Saline.

Group T: patients received Inj. Tramadol 0.5mg/kgBW IV diluted to 10ml in normal saline. Intraoperatively the temperature of the OT was maintained at 24±1°C for all the patients. Subarachnoid block was instituted at either L3-4 or L4-5 interspaces in sitting or lateral position using 3mL (15 mg) of hyperbaric bupivacaine 0.5% (with 8.5% dextrose) with 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 was assessed at 5-min intervals. Sensory block was assessed every 5 min till the level of block was established, and every 15 min thereafter. The core temperature was measured by a nasopharyngeal probe and surface temperature by an axillary probe.

Shivering was graded using a scale validated by Tsai and Chu: grade 0=no shivering, 1=piloerection but no visible shivering, 2=muscular activity in only one group, 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 120 min of surgery. The prophylaxis was regarded as ineffective if the patients exhibited grade 3 shivering any time during the study and then i.v. pethidine 25 mg was administered as a rescue drug.

Side-effects such as hypotension, nausea, vomiting, hallucinations and sedation were also recorded. Hypotension and bradycardia defined as a decrease in mean 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. Bradycardia was treated with atropine 0.01mg/kg BW. If any of the patients developed nausea and vomiting metoclopramide 10 mg was administered. Hallucination as a side-effect defined as a false sensory experience where the patients reported that they saw, heard, smelled, tasted or felt something that was non-existent was treated with midazolam 0.03mg/kg body wt. The attending anaesthetist also assessed the degree of sedation on a 5-point scale. 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. Motor block of the patient was assessed using Modified Bromage scale, 0 = No motor block; 1 = Can flex knee, move foot, but can't raise legs; 2 = Can move foot only; 3 = Cannot move foot or knee.

Postoperative:

Patients were observed for shivering in postoperative period, initially hourly for two hours then 2 hourly for next 4 hours. Post operatively patients were also monitored for any complications.

RESULTS:

The four groups were statistically comparable as regard to age, ASA class (1-2), sex, height, weight, level of block and duration of surgery, with p value>0.05 which was insignificant.

Table 1 : Demographic Profile of Patients

Variable	Group P		Group K		Group C		Group T		P value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age	43.10	13.22	41.47	15.74	41.83	13.05	40.80	14.58	0.936
Height	165.55	4.38	164.44	5.70	166.73	5.36	166.72	4.35	0.225
Weight	61.17	8.55	63.20	9.49	63.63	7.31	60.73	6.18	0.403
DOS	89.93	17.48	91.80	19.84	96.07	15.95	94.73	15.31	0.507
Gender (M/F)	21/9		20/10		21/9		22/8		0.957

ASA (I/II)	25/5	22/8	24/6		0.806
Median Level Blok	T7 (T3-T10)	T6 (T4-T10)	T7 (T4-T9)	T7 (T5-T10)	0.818

The preoperative vitals of four groups were comparable as regard to [HR, SBP, DBP, MAP, SP02, RR, TEMP.] with P value >0.05 which was insignificant. The four groups were intraoperatively statistically comparable with regard to [HR], during the first 30min the heart rate was higher in group K as compared to other three groups with P value <0.05 which was statistically significant, however after 30min the diff in heart rate between the four groups was insignificant with P value>0.05.

Showing incidence of different grades of shivering in the four groups

Table 2 : Showing incidence of different grades of shivering in the four groups

Shivering Grade	Group P		Group K		Group C		Group T		P value
	No.	%	No.	%	No.	%	No.	%	
Grade 0	8	26.7	25	83.3	28	93.3	26	86.7	<0.001*
Grade 1	3	10.0	1	3.3	1	3.3	1	3.3	0.551
Grade 2	2	6.7	1	3.3	0	0.0	1	3.3	0.559
Grade 3	17	56.7	3	10.0	1	3.3	2	6.7	<0.001*
Grade 4	0	0.0	0	0.0	0	0.0	0	0.0	-

Shows significant (P<0.05) decrease in shivering in all the other three groups as compared to placebo reinforcing the use of ketamine, Clonidine and tramadol in reducing shivering after anesthesia. The four groups were statistically comparable as regard to side effects like nausea, vomiting, hypotension and bradycardia, with p value>0.05 which was insignificant.

DISCUSSION

Our study has shown that prophylactic use of Ketamine, Clonidine and Tramadol were effective in preventing shivering during subarachnoid block without causing any untoward side effects. Ketamine is a competitive receptor antagonist of NMDA, which has a role in thermoregulation at various levels. It increases blood pressure, heart rate and cardiac output because of direct sympathetic stimulation and inhibition of norepinephrine uptake into post-ganglionic sympathetic nerve endings, and may decrease core to peripheral redistribution of heat. 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 postoperative shivering after regional and general anaesthesia¹⁵. Tramadol may cause nausea respiratory depression, tolerance and vomiting. Clonidine is a centrally acting alpha 2 agonist and the anatomic target of its anti-shivering effect can be found at three levels. It decreases the thermoregulatory threshold for vasoconstriction and shivering as the hypothalamus contains high-density alpha 2 receptors. It also reduces spontaneous firing in locus coeruleus-a pre-shivering centre in pons. The alpha 2 receptors also get activated to release dynorphine {opioid agonist}, nor epinephrine and acetylcholine. The depressor effects of these neurotransmitters at the dorsal horn modulate cutaneous thermal inputs in addition to noxious and mechanoreceptive transmission. Clonidine can cause hypotension and bradycardia as a side-effect. In our study, the incidence of shivering was 56.7% (in the placebo group). Our study was compared with various studies which were done from time to time.

Sagir et al. conducted a study in 2006 evaluated the effect of prophylactic i.v ketamine (0.5mg/kg), granisetron (3mg) and placebo before giving subarachnoid block and concluded that prophylactic use of 0.5mg/kg i.v ketamine was effective in preventing shivering developed during shivering. Dal et al in 2005 conducted a study evaluated the effect of normal saline, ketamine 0.5mg/kg and pethidine 20mg intravenously 20min before completion of surgery they concluded that prophylactic low dose ketamine was found to be effective in preventing postoperative shivering however there was no difference between the three groups regarding VAS pain scores.

Gangopadhyay et al in 2010 conducted a study to compare pethidine, tramadol and ketamine in prevention of shivering caused by subarachnoid block and also to compare their adverse effects. Patients received Group P (pethidine 0.4mg/kg), Group T (tramadol 1.0mg/kg) and Group K (ketamine 0.5mg/kg) intravenously just before giving spinal anaesthesia, they concluded that although pethidine, tramadol and ketamine effectively prevent shivering following spinal anaesthesia, the better haemodynamic stability and less adverse effect prove ketamine as a better alternative than other two drugs. Sia found clonidine to be an effective drug when used prophylactically at 1mcg/kg i.v to control shivering under neuraxial blockade. Tewari and others found oral clonidine 150mcg to be an efficacious drug in controlling shivering under neuraxial blockade. Dhorigol and others also found oral clonidine 150mcg to be effective in controlling shivering under subarachnoid block when used prophylactically.

Bilotta and Chan et al found tramadol to be promising drug in doses of 0.5mg/kg and 0.25mg/kg i.v., respectively, in controlling shivering under neuraxial blockade. Gangopadhyay and others found promising results with tramadol 1.0mg/kg i.v. in preventing shivering under spinal anaesthesia. 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. Ketamine causes a significant amount of sedation, which may be beneficial to us as it increases comfort, maintains cardiorespiratory stability, improves surgical conditions and prevents recall of unpleasant events during the surgery.

CONCLUSION

We conclude that giving Ketamine 0.5mg/kg, Clonidine 75mcg or tramadol 0.5mg/kg i.v. prophylactically just before subarachnoid block significantly decreased the incidence of shivering without causing any major side effects. Using ketamine may be more beneficial as it improves the hemodynamic profile by its sympathomimetic effects and it sedates the patient effectively, which increases patient comfort during surgery, maintains cardiorespiratory stability and prevents recall of unpleasant events during the surgery.

REFERENCES

1. Alojado ME, Ohta Y, Kemmotsu O. The effect of clonidine on the activity of neurons in the rat dorsal raphe nucleus in vitro. *Anesth Analg*. 1994;79:257-60.
2. Bilotta F, Pietropaoli P, Sanita R, Liberatori G, Rosa G. Nefopam and tramadol for prevention of shivering during neuraxial anesthesia. *Reg Anesth Pain Med*. 2002;27:380-4.
3. Chan AM, Ng KF, Tong EW, Jan GS. Control of shivering under regional anaesthesia in obstetric patients with tramadol. *Can J Anaesth*. 1999;46:253-8.
4. Dal D, Kose A, Honca M, Akinci SB, Basgul E, Aypar U. Efficacy of prophylactic ketamine in preventing postoperative shivering. *Br J Anaesth*. 2005;95:189-92.
5. De Witte J, Deloof T, De Veylder J, Housmans PR. Tramadol in the treatment of post anaesthetic shivering. *Acta Anaesthesiol Scand*. 1997;41:506-10.
6. Dhorigol MG, Dhulkhed VK, Biyani A, Desai N. Randomized controlled, double-blind study to evaluate oral clonidine to prevent post-subarachnoid block shivering in patients undergoing elective urologic surgery. *J Anaesthesiol Clin Pharmacol*. 2010;26:15-8.
7. Driessen B, Reiman W. Interaction of the central analgesic tramadol, with the uptake and release of 5-hydroxytryptamine in the rat brain in vitro. *Br J Pharmacol*. 1992;105:147-51.
8. Frank SM, Fleisher LA, Breslow MJ, et al. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events: A randomized clinical trial. *JAMA*. 1997;277:1127-34.
9. Gangopadhyay S, Gupta K, Acharjee S, Nayak SK, Dawn S, Pipl G. Ketamine, Tramadol and Pethidine in Prophylaxis of shivering during spinal anaesthesia. *J Anaesthesiol Clin Pharmacol*. 2010;26:59-63.
10. Hori T, Katafuchi T. Cell biology and the functions of thermosensitive neurons in the brain. *Prog Brain Res*. 1998;115.
11. Horn E-P, Sessler DI, Standl T, et al. Non-thermoregulatory shivering in patients recovering from isoflurane or desflurane anesthesia. *Anesthesiology*. 1998;89:878-86.
12. Ikeda T, Kazama T, Sessler DI, Toriyama S, Niwa K, Shimada C, et al. Induction of anesthesia with Ketamine reduces the magnitude of redistribution hypothermia. *Anesth Analg*. 2001;93:934-8.
13. Krause T, Tonner PH, Scholz J, Schweers S, Schulte am Esch J. Interaction of tramadol with cerebral alpha2-adrenoceptors. Possible role in attenuation of postoperative shivering. *Anesthesiology*. 1999;91:A-388.
14. Kurz A, Sessler DI, Narzt E, et al. Postoperative hemodynamic and thermoregulatory consequences of intraoperative core hypothermia. *J Clin Anesth*. 1995;7:359-366.
15. Mahajan RP, Grover VK, Sharma SL, Singh H. Intraocular pressure changes during muscular hyperactivity after general anesthesia. *Anesthesiology*. 1987;66:419-421.
16. Matsukawa T, Sessler DI, Christensen R, Ozaki M, Schroeder M. Heat flow and distribution during epidural anesthesia. *Anesthesiology*. 1995;83:961-967.
17. Nishiyama T, Yokoyama T, Hanaoka K. Sedation guidelines for midazolam infusion during combined spinal and epidural anesthesia. *J Clin Anesth*. 2004;16:568-72.
18. Panzer O, Ghazanfari N, Sessler DI, et al. Shivering and shivering-like tremor during labour with and without epidural analgesia. *Anesthesiology*. 1999;90:1609-16.
19. Powell RM, Buggy DJ. Ondansetron given before induction of anesthesia reduces shivering after general anesthesia. *Anesth Analg*. 2000;90:1423-7.
20. Rosa G, Pinto G, Orsi P, et al. Control of post anaesthetic shivering with nefopam hydrochloride in mildly hypothermic patients after neurosurgery. *Acta Anaesthesiol Scand*. 1995;39:90-95.
21. Sagor O, Gulhas N, Toprak H, Yucel A, Begec Z, Ersoy O. Control of shivering during regional anaesthesia: Prophylactic ketamine and granisetron. *Acta Anaesthesiol Scand*. 2007;51:44-9.
22. Sessler DI, Rubinstein EH, Moayeri A. Physiological responses to mild perianesthetic hypothermia in humans. *Anesthesiology*. 1991;75:594-610.

23. Sessler DI. Temperature monitoring. In: Miller R.D, editors. *Anesthesia*. Philadelphia: PA Lippincott, 1990: 1227-1242.
24. Sia S.I.v. clonidine prevents post-extradural shivering. *Br J Anaesth*. 1998;81:145-6.
25. Tewari A, Katyal S, Singh A, Garg S, Kaul TK, Narula N. Prophylaxis with oral clonidine prevents perioperative shivering in patients undergoing transurethral resection of prostate under subarachnoid block. *Indian J Urol*. 2006;22:208-12.