Prevention of Shivering during Spinal Anesthesia: Comparison between Tramadol, Ketamine and Ondansetron

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ABSTRACT

Introduction: Shivering is an unpleasant experience after spinal anesthesia. We conducted this study to evaluate the efficacy of ondansetron, ketamine and tramadol for prevention of shivering.

Methods: In this randomized controlled study, 120 patients aged 18-65 years of American Society of Anesthesiologist (ASA) physical status I and II undergoing various surgical procedures were included and allocated alternately to one of the 4 groups; Normal saline (Group1), Ondansetron 4mg (Group2), Ketamine 0.25mg/kg (Group3) and Tramadol 0.5mg/kg (Group4). Incidence of shivering, effect on hemodynamics, nausea, vomiting, sedation and emergence reactions were recorded. Data was analyzed using SPSS (The Statistical Package for Social Sciences) version 20.0 software.

Results: The patients were comparable in terms of demographic variables, baseline temperature, type of surgery, median level of sensory blockade, duration of surgery and anesthesia. Shivering was present in 17 (56.7%), 5 (16.7%), 3 (10%) and 3 (10%) patients respectively in Group 1, 2, 3 and 4 which was statistically significant when compared to Group 1 (P=0.00) The odds of NS and ondansetron, NS and ketamine, NS and tramadol was 6.53, 11.76 and 11.76 respectively which showed that study drugs were effective in preventing shivering. None of the patients were sedated in Group 1 and 2. Mild to moderate sedation was present in Group 3 and 4 (P=0.00). None of the patients had drug related adverse reactions.

Conclusions: Prophylactic use of ondansetron, low doses of ketamine and tramadol is effective in preventing shivering post spinal anesthesia without untoward effects.

Keywords: *Anesthesia spinal; Ketamine; Ondansetron; Shivering; Tramadol.*

INTRODUCTION

Shivering is very common after spinal anesthesia with incidence of 55%.[1] Hypothermia which occurs after spinal anesthesia is due to vasodilation below the level of block and redistribution of body heat from core to periphery and restriction of shivering to muscle mass above the level of blockade.[2]

The aim of the study was to find the effectiveness of ondansetron, ketamine and tramadol in preventing shivering. We conducted this study because shivering is an unpleasant experience which leads to patient discomfort. Therefore it is necessary to monitor and maintain normothermia under anesthesia.

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The objective of the study was to evaluate anti-shivering efficacy of ondansetron, ketamine and tramadol and effect of these drugs on hemodynamics, arterial oxygen saturation, axillary temperature, nausea, vomiting and sedation.

METHODS

This randomized controlled study was carried out in the Department of Anesthesia of Manipal College of Medical Sciences from July 2015 to June 2016 after obtaining clearance from the institutional research committee and written informed consent from the patients. Patients undergoing elective general, gynecological and orthopedic surgery were enrolled in the study and patients with known hypersensitivity to the study drug, pregnancy, thyroid disease and severe cardiopulmonary disease were excluded from the study. Total of 120 adult patients of American Society of Anesthesiologist (ASA) physical status I&II, aged 18-65 years were enrolled in the study. The patients were allocated to one of the 4 groups: Normal saline (Group 1), Ondansetron 4 mg (Group 2), Ketamine 0.25 mg kg^{-1} (Group 3) and tramadol 0.5 mg kg^{-1} (Group 4) and each group contained 30 patients.

Independent t-test was used for quantitative data for comparison between two groups, one-way ANOVA for quantitative data comparison between four groups, Kruskal–Wallis H-test for quantitative nonparametric data between four groups and chi square for categorical data. The P value ≤ 0.05 was considered significant. Data was analyzed using SPSS (The Statistical Package for Social Sciences) version 20.0 software.

Patients were shifted to the operation theatre and ASA standard monitors attached. Baseline heart rate (HR), noninvasive blood pressure (NIBP), mean arterial pressure (MAP), oxygen saturation (SPO2), electrocardiography (ECG), and axillary temperature were recorded. Venous access was secured with 18G cannula and ringer lactate was started at 15 ml/kg during spinal anesthesia and maintained at 6 ml/kg/h after spinal anesthesia.

Under aseptic conditions and adequate local infiltration subarachnoid block was performed with 0.5% heavy bupivacaine (15 mg) at L3-4/L4-5 interspace using 25G Quincke's needle via midline approach in lateral decubitus position. Immediately after the intrathecal injection, one of the study drugs were given as IV bolus. All the drugs were reconstituted to the volume of 5 ml. Operation theatre temperature was maintained at 22 °C. Patients were covered with drapes and IV fluids were administered at room temperature. Supplemental oxygen was given via face mask at the rate of 5 l/min.

Vital parameters such as HR, NIBP, MAP, SPO2 and axillary temperature were recorded at intervals of every 5 min for first 30 min and every 15 min till the end of surgery. ECG was monitored continuously throughout the procedure. Level of sensory blockade was assessed using pinprick sensation immediately after intrathecal administration of drug and every 5 mins for the first 15 minutes and the block height was recorded.

The scale proposed by Crossley and Mahajan was used to grade shivering.[3]

Table 1. Grades of shivering.

0 = no shivering;		
1	=	One or more of the following: piloerection, peripheral vasoconstriction, peripheral cyanosis with no other cause, but no muscle activity
2	=	visible muscular activity confined to one muscle group
3	=	visible muscular activity in more than one muscle
4	=	gross muscular activity involving the whole body

Patients with shivering of grade 1 and 2 were categorized as mild and moderate shivering respectively, whereas grade 3 and 4 shivering were categorized as severe shivering. The onset of shivering (time in minutes of the occurrence of shivering after institution of spinal anesthesia), grade of shivering, nausea, vomiting, sedation, hallucination, tachycardia, hypotension, oxygen desaturation and respiratory depression were recorded.

After the prophylactic administration of one of the study drugs, if the patients shivered for ≥ 15 minutes to at least grade 3, prophylaxis was considered to be ineffective and Pethidine 0.5mg kg^{-1} was given as rescue medication. Injection metoclopramide 10 mg was given for vomiting.

Sedation was assessed on 5 point scale where 1: fully awake and oriented patient, 2: drowsy, 3: eyes closed, arousable on command, 4: eyes closed, arousable to physical stimuli, 5: eyes closed and patient unarousable to physical stimuli.

RESULTS

The study was conducted in 120 patients, 30 in Group 1(NS), 30 in Group 2 (Ondansetron), 30 in Group 3 (Ketamine) and 30 in Group 4 (Tramadol).

The axillary temperature was measured every 5 min for first 30 min and every 15 min till the end of surgery. The onset of shivering was noted early in Group 1 which was statistically significant when compared with other groups (Table 1). Decrease in axillary temperature was noted in all 4 groups after spinal anesthesia however statistically significant difference was observed at 30,45,60,75 and 90 mins with respective P values of 0.04, 0.00, 0.00, 0.05, and 0.01.

The incidence of shivering was highest in Group 1 followed by the patients in Group 2 whereas the patient in Group 3 and 4 had equal incidences. It was statistically significant when compared to Group 1 (Table 2). When we evaluated the odd ratio of NS and ondansetron we found that patients receiving NS shivered 6.53 times more than those treated with the ondansetron. Similarly, odds of NS and ketamine, NS and tramadol was 11.76 which clearly showed that patients given NS shivered 11.76 times more than those treated with ketamine and tramadol (Table 2).

Table 1. Onset of shivering.

	Group1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 30)	Group 4 (n = 30)
Onset of shivering (mean ± sd)	13 ± 9.62	21 ± 1.15	18.33 ± 2.88	16.67 ± 10.41
p value	-	0.00 *	0.01*	0.04*

*n = number of patients, Data presented as mean±SD, *significant P value when compared with group 1 (P value ≤0.05 considered as significant)*

Adverse effects associated with drugs such as nausea, vomiting and hypotension were absent in all the 4 groups. Emergence reaction was not observed even in Group 3. Sedation was absent in Group 1 and Group 2 whereas patients in Group 3 and 4 had mild sedation to moderate sedation. It was statistically significant when compared to Group 1 (Table 3).

The patients were comparable in terms of age, gender, body mass index (BMI) and ASA physical status (Table 4).

Similarly, there was no difference among the groups in terms of baseline temperature, type of surgery performed, duration of surgery, duration of anesthesia and median level of sensory blockade (Table 5).

Table 2. Incidence of shivering in study groups.

Shivering	Group 1 n = 30	Group 2 n = 30	Group 3 n = 30	Group 4 n = 30
Present (n/%)	17/56.7	5/16.7	3/10	3/10
Absent (n/%)	13/43.3	25/83.3	27/90	27/90
Chi square	-	10.33	14.7	14.7
Odds ratio	-	6.53	11.76	11.76
p value	-	0.00 *	0.00 *	0.00 *

n = number of patients, data presented as number of patients and percentage, P value ≤0.05 considered as significant

Table 3. Grade of sedation.

Sedation grade	Group1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 30)	Group 4 (n = 30)
1	30 (100%)	30 (100%)	23 (76.67%)	19 (63.33%)
2	0	0	6 (20%)	9 (30%)
3	0	0	1 (3.33%)	2 (6.67%)
4	0	0	0	0
5	0	0	0	0
Median (Range)	1 (1-1)	1 (1-1)	1 (1-3)* 0.00	1 (1-3)† 0.00

*n = number of patients, Data presented as mean±SD, *significant P value when compared with group 1 (P value ≤0.05 considered as significant), *significant when compared to group 1 and 2, †significant when compared to group 1 and 2*

Table 4. Demographic variables of patients enrolled in the study.

Parameter	Group 1 n = 30	Group 2 n = 30	Group 3 n = 30	Group 4 n = 30	p value
Age (years)	37.93 ± 16.88	37.63 ± 16.36	38.26 ± 14.65	42.3 ± 16.77	0.65
Male/Female (n)	23/7	19/11	17/13	19/11	0.48
BMI (kg/m²)	22.62 ± 3.75	22 ± 2.75	23.02 ± 3.74	24.02 ± 4.37	0.18
ASA I/II (n)	26/4	25/5	25/5	28/2	0.65

Data presented as mean±SD, n = number of patients; SD= standard deviation, P value ≤0.05 considered as significant

Table 5. Type of operation, duration of surgery, duration of anesthesia, median level of sensory blockade and baseline axillary temperature.

Parameter	Group 1 n = 30	Group 2 n = 30	Group 3 n = 30	Group 4 n = 30	p value
General surgery/ Orthopedics / Gynecology (n)	19/10/1	14/14/2	16/13/1	17/12/1	0.31
Duration of surgery (min)	54.50 ± 35.58	63.17 ± 38.58	66.67 ± 8.22	54.17 ± 35.13	0.46
Duration of anesthesia (min)	59.80 ± 35.17	68.17 ± 38.58	71.6 ± 38.18	59.17 ± 35.17	0.47
Median level of sensory blockade	T7	T7	T7	T7	0.92
Baseline temperature (°C)	34.6 ± 1.35	34.03 ± 1.82	34.03 ± 1.16	34.32 ± 1.42	0.44

n = number of patients, data presented as mean±SD, min = time in minutes, P value ≤0.05 considered as significant

DISCUSSION

Shivering occurs frequently after neuraxial anesthesia with incidence ranging from 40-60%. In our study, the incidence of shivering in Group 1 was 56.7% which is similar to previous studies.[4,5] Ways to prevent intraoperative hypothermia include various non pharmacological and pharmacological methods. Different drugs that are used for prevention and treatment of shivering includes opioids, nonopioid analgesics, 5-HT3 antagonists, α adrenoceptor agonists and cholinomimetic agents. These drugs are not void of adverse effects thus the search continues for drug which is effective in preventing and treating shivering with negligible side effects.

Ondansetron is a 5HT3 receptor antagonist; commonly used for its antiemetic property in the perioperative period. It is also considered safe and effective for the prevention of post anesthesia shivering in the dosage of 4-8 mg. The antishivering property could be attributed to inhibition of serotonin reuptake on the preoptic anterior hypothalamic region. 5-HT3 receptors also influence both heat production and heat loss pathways. In our study the incidence of shivering after prophylaxis with ondansetron was 16.7% which is similar to those confirmed by other investigators[6-8] whereas it is in contrast with the study conducted by Browning et al. This is because the study was conducted using combined spinal epidural in young parturient female. The underlying mechanism of shivering in parturient might be different than other population.[6] In this study we found that shivering in NS group is 6.53 times more than in the ondansetron group which is similar to the findings of Shakya et al.[7] None of the patients in our study had drug related side effects as bradycardia and hypotension which is in concordance with the past studies.[7]

Ketamine categorized as a dissociative anesthetic is a non-competitive antagonist of N-methyl D-aspartate (NMDA) receptor which in sub anesthetic doses has a role in thermoregulation. Ketamine controls shivering by non-shivering thermogenesis either by the action on the hypothalamus or by the β-adrenergic effect of norepinephrine. NMDA receptor also modulates the noradrenergic and serotoninergic neurons in the locus coeruleus which might contribute in regulating

temperature. Most of the studies of ketamine has been conducted using doses of ≥0.5mg/kg. Studies have shown that ketamine in the dosage of 0.5-0.75 mg/kg is more potent than pethidine (25mg) for the prevention and treatment of shivering.[8,9] However the associated side effects limits its use. Thus in the present study we used low dose of ketamine (0.25mg/kg) and observed that there were no associated emergence reactions as hallucination, delusion, illusion, extracorporeal sensation, arterial O_2 desaturation, respiratory depression, nausea, vomiting, hypertension and tachycardia which is similar to past studies.[10] In the study conducted by Sagir et al.[11] none of the patients had shivering which is in contrast with our findings (10%). This may be due to the higher dose used in their study. Similarly Hidayah et al. in their study have reported the incidence of shivering with 0.5 mg/kg ketamine to be 8%. This might be due to the higher dose of ketamine and intrathecal use of fentanyl (25 ug)[12] because intrathecal fentanyl reduces shivering by 30%.[13] Thus 10% incidence of shivering in the present study might be comparable to those findings by the previous investigators as we have used ketamine in lower dose of 0.25 mg/kg to achieve the desired effect and minimize adverse effects.

Tramadol is a synthetic opioid which regulates temperature at various level. It inhibits the reuptake of serotonin and norepinephrine in the spinal cord which facilitates the release of serotonin. Its action at kappa, opioid and α 2 adrenoceptor also produce anti shivering effect.[14] Tramadol in doses of 0.5-3mg/kg have been found to be effective in controlling post-operative shivering with equal efficacy as that of 0.5 mg/kg pethidine with negligible side effects.[15,16] In the present study prophylaxis with 0.5mg/kg tramadol decreased the incidence of shivering by 46.7% as compared to those patients receiving NS and the incidence of shivering was only 10% which is similar to results concluded by previous investigators. Past studies have reported the incidence of shivering with tramadol ranging from 8.8 to 16%.[17] None of the patients experienced drug related side effects as nausea and vomiting. This is probably because of low dose used in the study. Similarly none of the patients had hypotension, respiratory depression and arterial oxygen desaturation. Patients were sedated to only grade 2. None of the patients experienced deep and intense level of sedation. Mild to moderate level of sedation is actually desired intraoperatively to allay anxiety and intraoperative awareness.

One of the important finding of our study was decrease in the incidence of shivering by 40% and 46.7%, 46.7% after prophylaxis with ondansetron, ketamine and tramadol respectively with negligible side effects. One of the limitations of our study was failure to measure core temperature. However the axillary temperature may be used as a surrogate to core temperature, except in extreme body temperature changes.[18]

CONCLUSIONS

The present study suggests that prophylactic use of ondansetron and low doses of ketamine and tramadol as an effective way of preventing shivering post spinal anesthesia and thus recommends its use. In our study we noticed that in the patients in whom the prophylaxis with the study drugs failed pethidine 0.5 mg/kg could stop them from shivering. This is probably due to the different mechanism of action of pethidine.

Conflict of Interest: None.

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