A STUDY OF PROPHYLACTIC LOW DOSE KETAMINE AND GRANISETRON FOR PREVENTION OF SHIVERING DURING SPINAL ANESTHESIA

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ABSTRACT

Spinal anesthesia significantly results in shivering and hypothermia as unwanted effect. Shivering increases oxygen consumption which may be deleterious in patients who have low cardiac and pulmonary reserve. We conducted this study to evaluate the efficacy of Ketamine and Granisetron for prevention of shivering under spinal anesthesia. In this randomized prospective study, 90 Patients aged 18-60 years of ASA physical status I and II undergoing various surgical procedures were included and allocated alternately to one of the 3 groups; Normal saline (Group P), Ketamine 0.25 mg/kg (Group K) and Granisetron 40µg/kg (Group G). Incidence of shivering, effect on haemodynamics, nausea, vomiting, and sedation were recorded. The patients were comparable in terms of demographic variables, baseline temperature, and median level of sensory blockade. Shivering was present in 10 (33%), 3 (10%), 1 (3%) respectively in Group P, G, K. In Group P, 8 (26%) patients experienced shivering at Grade 3 and this was significantly higher than Groups G and K (P = 0.0003). None of the patients were sedated in Group G and P. The sedation was seen in 8 cases (26%) in Ketamine group, most of them were sedated to grade 2 and only 3 were of grade 3 (P<0.05). No hallucination was seen in any of the patients. Low dose ketamine and Granisetron are effective for prevention of shivering in comparison to placebo during spinal anesthesia and ketamine is more effective than granisetron.

KEYWORDS

Shivering, ketamine, granisetron, spinal anesthesia

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INTRODUCTION

Humans are homoeothermic species, a thermoregulatory system coordinates defenses against cold and heat to maintain internal body temperature within a narrow range from 36.5°C to 37.5° and optimize normal physiologic and metabolic function.[1] Thermal inputs are integrated at the level of the anterior hypothalamus, which compares peripheral information with a threshold value, or the set-point. Temperatures higher than this set point will trigger responses to cool the body, while temperatures lower than this set point will activate reflexes to warm the body.[2]

Both general and regional anesthesia is known to affect the efficiency of this homeostatic system and may result in different degrees of perioperative hypothermia.[2,3] There are three principal reasons for hypothermia under spinal anesthesia. First, spinal anesthesia decreases hypothalamic threshold by 0.5°C, triggering vasoconstriction and shivering above the level of block.[2] This reduction in threshold is proportional to the number of spinal segments blocked, advanced age and high-level spinal blockade.[3] Secondly, loss of thermoregulatory vasoconstriction below the level of the spinal block, leads to increased heat loss from body surfaces. Lastly, spinal anesthesia leads to an internal redistribution of heat from the core to the peripheral compartment.[4]

The incidence of shivering is up to 40-60% in regional anesthesia. Shivering causes increased metabolic activity and increased oxygen consumption by up to 100%. It increases cardiac output, peripheral resistance, carbon dioxide production and lactic acidosis.[5] It also causes arterial hypoxia and has been shown to correlate with increased risk of myocardial ischemia. It also increases intracranial and intraocular pressure. Moreover, it interferes with ECG and oxygen saturation monitoring (pulse oximetry).[6]

The approach to maintaining perioperative normothermia, based on the principle of prevention, has recently been proposed. Selection of proper body temperature monitoring system is the primary step.[7] Environmental temperature and humidity are important determining factors in the maintenance of core temperature. Relative humidity of greater than 45% with an operating room temperature ranging between 21^0C and 24^0C is usually recommended for adult patients, whereas for children the temperature should be raised to 24-26^0C.

Various non pharmacological and pharmacological ways to prevent intraoperative shivering have been used. Different drugs that are used for prevention and treatment of shivering includes opioids, nonopioid analgesics, 5-HT3 antagonists, and α adrenoceptor agonists.[8,9] However, there are some reported specific side-effects of these agents including hypotension, hypertension, sedation, respiratory depression, nausea and vomiting.[8,9] A variety of physical (radiant heaters, increased ambient temperature, and space blankets)[10] and pharmacological methods have been tested in reducing peri-operative hypothermia and suppressing post-anesthetic shivering; however, none of these have received universal acceptance.[11,12]

Regional anesthesia produces vasodilatation, which facilitates the core-to-peripheral redistribution of heat.[13] Ketamine, a competitive NMDA receptor antagonist has a role in thermoregulation at various levels. NMDA receptor modulates noradrenergic and serotoninergic neurons in locus coeruleus. It increases blood pressure, heart rate, and cardiac output because of direct central sympathetic stimulation and inhibition of norepinephrine uptake into preganglionic sympathetic nerve endings, and may decrease core-to-peripheral redistribution of heat.[14] Thus, it appears logical to use ketamine in patients who are at risk of hypothermia. Ketamine, given intravenously (IV.), appeared quite useful in reducing shivering during regional anesthesia but patients developed hallucinations and post-operative vomiting when higher doses were used.[15]

Serotonin (5-hydroxytryptamine), a biological amine found in the brain and spinal cord, has a role in neurotransmission.[16] Indeed, Tramadol, which inhibits 5-HT reuptake, and ketanserin, a 5-HT2 antagonist, inhibit established post-anesthetic shivering.[9] All these observations suggest that the serotonergic system has a role in the control of post-anesthetic shivering. During regional anesthesia, granisetron, a 5-HT3 receptor antagonist, has been shown to be effective in the prevention of emetic symptoms in dose of 40μg/kg IV.[17] There is only few study regarding the use of granisetron as a prophylactic agent against post-operative shivering.

Hence we conducted the present study to evaluate and compare the relative efficacy and safety of low dose ketamine and granisetron for prevention of shivering during spinal anesthesia.

MATERIALS AND METHODS

All patients were assessed in the ward in the evening prior to surgery to study the fitness and relevant laboratory parameters was evaluated and informed consent was taken after explaining the procedure to them. All the patients were kept on fasting for 8 hours.

In the operation theatre a peripheral line with 18 gauge cannula was placed and standard monitoring including lead II electrocardiography, pulse oximetry and noninvasive blood pressure (BP) was started. Baseline values of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) and percentage of arterial oxygen saturation were recorded. Before the spinal anesthesia procedure, each patient received 10 ml/kg lactated Ringer's solution. Subarachnoid anesthesia was instituted at either L3/4 or L4/5 interspaces with 3ml hyperbaric 0.5% bupivacine, followed by either I.V. ketamine 0.25 mg/kg in group K or granisetron I.V 40 mcg/kg in group G or saline in group P.

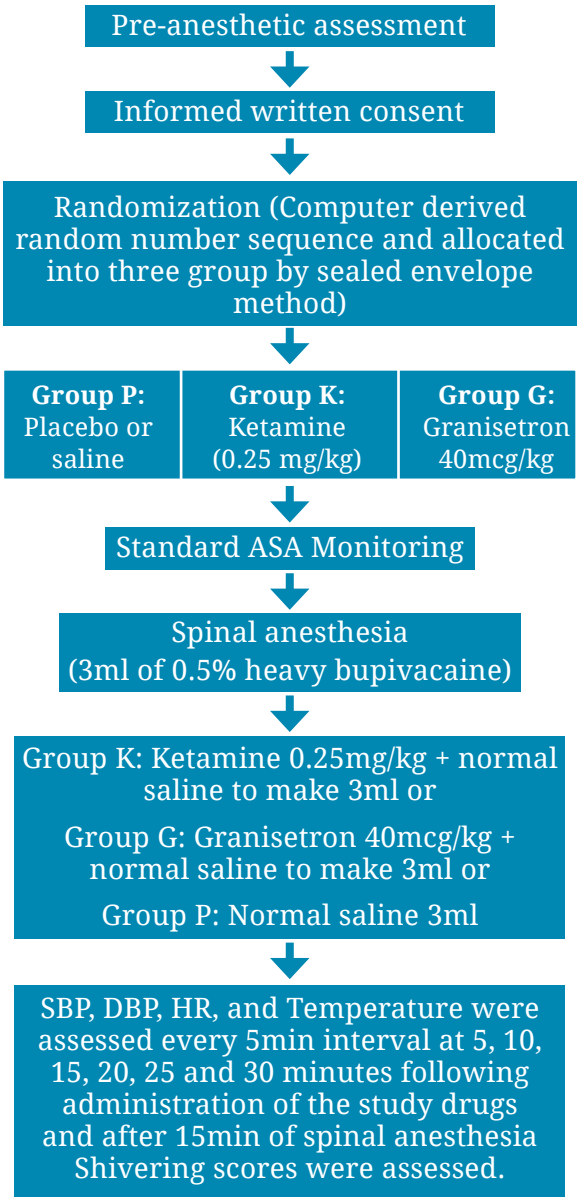

Fig. 1: Graphic representation of study design and procedure

BP, SPO2, HR, and temperature, were assessed every 5min interval. After 15min of spinal anesthesia Shivering score were assessed every 5min interval using Tsai and Chu scale (Table 1). Patients with shivering score of 3 or more, was given I.V. meperidine 0.5 mg/kg as rescue drug.

Table 1: Tsai and Chu shivering scale[8]

Scale	
0	No shivering
1	Piloerection or peripheral vasoconstriction but no visible shivering (mild)
2	Muscular activity in only one muscle group
3	Muscular activity in more than one muscle group but not generalized (severe)
4	Shivering involves whole body

Body temperature was monitored with a tympanic non-invasive thermosan thermometer and an axillary thermometer at the start of spinal anesthesia and intraoperatively. The temperature of the operating room was maintained between 21°C and 23°C.

Side effects like nausea, vomiting, hallucinations, hypotension, and sedation were recorded. Degree of sedation was assessed and graded according to Ramsay's sedation score[18] (Table 2).

Hypotension was defined as a decrease in mean blood pressure (MBP) of more than 20% from

Table 2: Ramsay's sedation scale

Scale	
1	Awake and anxious, agitated, or restless
2	Awake, cooperative, oriented, tranquil
3	Awake, responds to commands
4	Asleep, brisk response to light glabellar tap or loud noise
5	Awake, sluggish response to light glabellar tap or loud noise stimulus
6	Asleep, no response to light glabellar tap or loud noise

baseline. This was treated with Increased rate of infusion of IV fluid (200 ml of crystalloid) over 3 min, if this failed to increase blood pressure then Inj. Mephentermine 3 mg IV bolus dose was given. The amount of Mephantermine given in each group was recorded. For bradycardia (HR<50 beats/min): Inj. Atropine 0.6 mg IV bolus dose was given.

If patients developed nausea and vomiting, IV Metoclopramide 10 mg was administered. 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 sample size was calculated using following formula

$$n = \frac{2\bar{P}(1-\bar{P})F}{D^2}$$

$\bar{P}$ = pooled prevalence = 0.4[19], The minimum sample size calculated was 24 in each group. Hence 30 cases was taken in each group. All data were entered in Microsoft office Excel worksheet 2013 and statistical analysis was performed using Microsoft® excel® 2013. Descriptive statistics was used for describing the data (i.e mean, SD, etc). The data among groups were compared using one-way ANOVA. The within-group data were analysed using repeated-measures analysis of variance followed by Bonferroni's post-hoc testing. The incidence of shivering and side-effects were compared using the Chi-square test. The results were reported as mean ± standard deviation. P < 0.05 was considered statistically significant.

RESULTS

A. Demographic Profile:

There were 22 male and 8 female in Granisetron group, 23 male and 7 female in Ketamine group and 21 male and 9 female in Placebo group. The three groups were comparable with respect to distribution of male and female patients.

Haemodynamic Parameters: Mean initial values of diastolic BP were comparable in the three groups. Mean diastolic blood pressure decreased from baseline in Granisetron and placebo group. However in Ketamine group mean diastolic blood pressure increased in first 15min from baseline (P <0.05).

Mean diastolic blood pressure was higher in first 15min in ketamine group as compared to Granisetron group (P <0.05). Mean systolic blood pressure decreased from baseline in Granisetron and placebo group. However in ketamine group mean systolic blood pressure increased from baseline (P >0.05).

No significant changes in mean systolic blood pressure was found in Granisetron Group compared to ketamine group (P >0.05). Increase in heart rate in first 15min was noticed in ketamine group compared to baseline (P <0.001) which was higher in comparison to Placebo group (P=0.0118) and Granisetron group (P= 0.0003).

Mean axillary temperature decreases significantly in Group P from baseline value after spinal anesthesia beginning from the 10th min (P <0.001). The axillary body temperatures in group K was significantly higher than Groups P (P <0.001) and Group G (P <0.05) in the 10th to 50th min interval.

Table 3: Comparison of gender distribution between three groups

Gender	Groups			Total	P value
	Group G	Group K	Group P		
Male	22 (73%)	23 (76%)	21 (70%)	66	0.84
Female	8 (27%)	7 (24%)	9 (30%)	24	
Total	30	30	30	90	

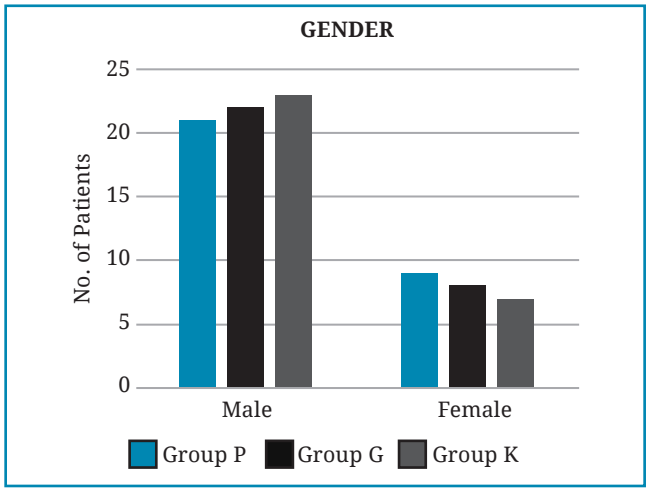

Fig. 2: Comparison of gender distribution between three groups

Haemodynamic Parameters

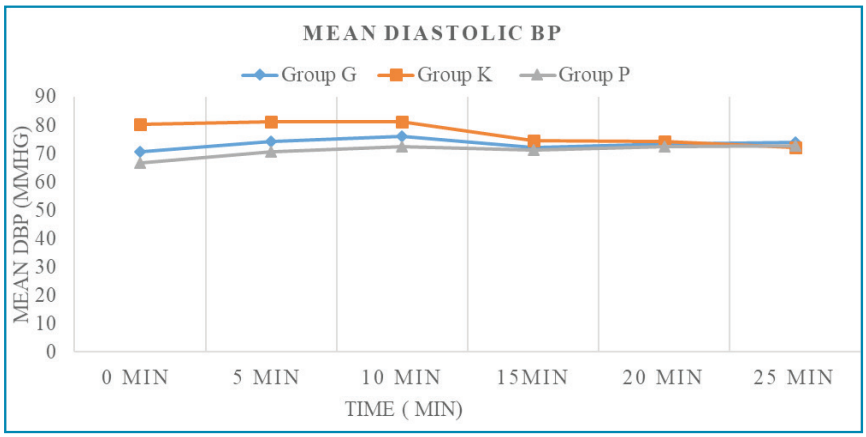

Fig. 3: Comparison of mean diastolic blood pressure between the three groups.

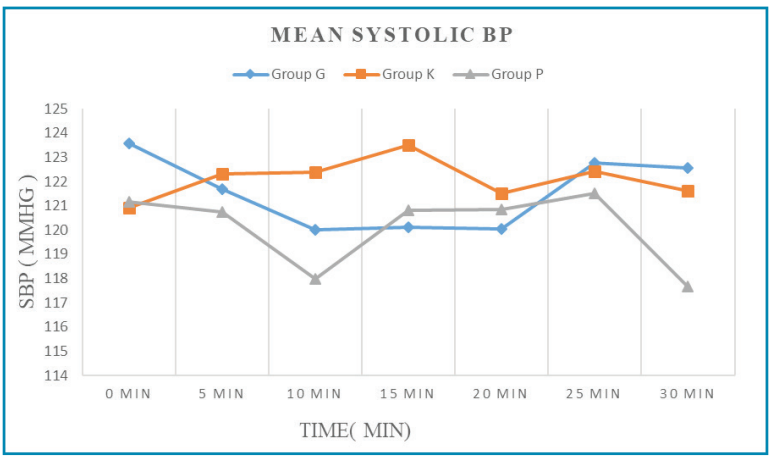

Fig. 4: Comparison of mean systolic blood pressure between three groups

Table 4: Patient characteristics

	Group G (n=30)	Group K (n=30)	Group P (n=30)	P value
Mean age years ± SD	38.50 ± 12.26	33.90 ± 14.16	36.03 ± 13.14	0.312
Mean height (cm) ± SD	167.64 ± 6.98	167.11 ± 9.08	162.53 ± 10.36	0.054
Mean weight (kg) ± SD	63.77 ± 12.36	63.47 ± 8.37	69.80 ± 14.68	0.084
ASA I/II (n)	25/5	27/3	27/3	
Median level of sensory block (dermatome)	T6 (T5- T8)	T6 (T5-T8)	T6 (T5-T8)	

ASA physical status grading and median level of sensory block.

All patients in all the 3 groups had decrease in core temperature from baseline value after spinal anesthesia (P <0.001).The decrease in core temperature seen in Group P was significantly more than Group K (P <0.05) and Group G (P <0.05) beginning from the 15th min. There was no significant difference in mean core temperature at various time points between Groups K and G (P =0.315).

Shivering at grade 4 was not observed in any patients. 8.8% of patient (8/90) experienced shivering at grade 3 and requested treatment. In group P, 8 out of 30 patients experienced shivering at grade 3 and this was significantly higher than groups G and K (P =0.0003).

10% of patient (3/30) in Granisetron and 3% of patient (1/30) in ketamine group experienced shivering at grade 02. The incidence of shivering was significantly higher in granisetron (G) group as compared to Ketamine (K) group (P < 0.05).

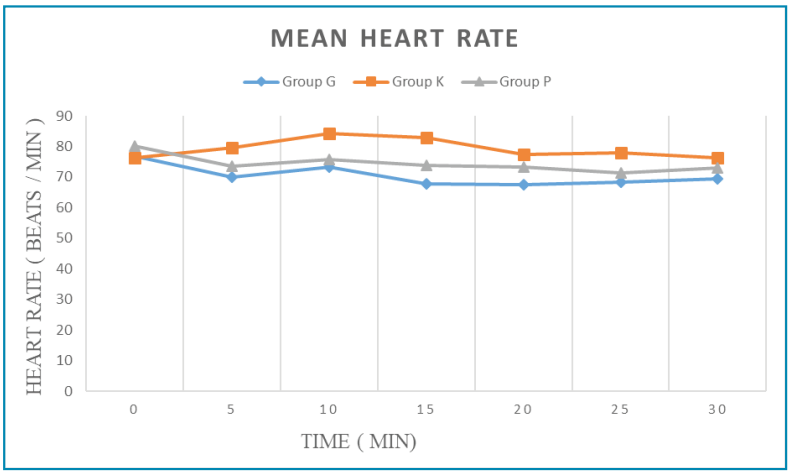

Fig. 5: Comparison of mean heart rate between three groups.

Table 5: Mean diastolic BP (mmHg) in three groups and statistical comparison (between groups)				
***Time(Min)**	**Group G**	**Group K**	**Group P**	**P value**
0	74.8 ± 11.0	76.7 ± 11.64	73.3 ± 10.71	
5	70.50 ± 9.68	80.33 ± 13.57	66.67 ± 6.86	
10	74.33 ± 11.19	81.17 ± 11.42	70.50 ± 8.64	
15	76.00 ± 10.93	81.17 ± 11.94	72.33 ±10.06	0.0026
20	72.17 ± 10.39	74.67 ± 10.16	71.17 ± 7.27	
25	73.50 ± 9.20	74.17 ± 8.51	72.50 ±11.35	
30	73.83 ± 9.34	72.17 ± 8.77	72.67± 8.58	

*Mean Diastolic BP ± SD, * Minutes after drug administration*

Table 6: Mean diastolic BP (mmHg) in groups G and K and statistical comparison			
Time (Min)	**Group G**	**Group K**	**P value**
0	74.8 ± 11.0	76.7 ± 11.64	
5	70.50 ± 9.68	80.33 ± 13.57	
10	74.33 ± 11.19	81.17 ± 11.42	0.016
15	76.00 ± 10.93	81.17 ± 11.94	
20	72.17 ± 10.39	74.67 ± 10.16	
25	73.50 ± 9.20	74.17 ± 8.51	
30	73.83 ± 9.34	72.17 ± 8.77	

Mean Diastolic BP ± SD

Table 7: Mean systolic blood pressure (mmHg) in the three groups and statistical comparison (between groups)				
***Time (Min)**	**Group G**	**Group K**	**Group P**	**P value**
0	123.57 ± 12.70	120.93 ± 12.95	121.17 ± 12.02	
5	121.67 ± 11.66	122.33 ± 16.69	120.73 ±15.29	
10	120.00 ± 14.44	122.37± 15.58	118.00 ±10.79	
15	120.13 ± 12.03	123.50 ± 13.23	120.80 ± 12.01	0.077
20	120.03 ± 15.85	121.50 ± 15.09	120.83± 12.95	
25	122.77 ± 12.95	122.43 ± 12.93	121.50 ±10.66	
30	122.57 ± 15.33	121.63 ± 14.84	117.67 ±15.29	

*Minutes after drug administration, initial values of mean systolic BP were comparable in the three groups.

Table 8: Mean systolic blood pressure (mmHg) i groups G and K and their statistical comparison			
Time (Min)	**Group G**	**Group K**	**P-value**
0	123.57 ± 12.70	120.93 ± 12.95	0.153
5	121.67 ± 11.66	122.33 ± 16.69	
10	120.00 ± 14.44	122.37± 15.58	
15	120.13 ± 12.03	123.50 ± 13.23	
20	120.03 ± 15.85	121.50 ± 15.09	
25	122.77 ± 12.95	122.43 ± 12.93	
30	122.57 ± 15.33	121.63 ± 14.84	

Table 9: Mean heart rate in the three groups and statistical comparison				
Time (Min)	**Group G**	**Group K**	**Group P**	**P-value**
0	76.73 ± 15.38	76.23 ± 10.65	80.2 ± 11.42	0.0002
5	70 ± 10.25	79.5 ± 12.55	73.5 ± 9.83	
10	73.23 ± 14.13	84.27 ± 12.13	75.83 ± 10.59	
15	67.83 ± 13.24	82.93 ± 11.38	73.77 ± 9.64	
20	67.5 ± 11.94	77.33 ± 12.43	73.17 ± 8.75	
25	68.33 ± 12.18	78 ± 9.87	71.33 ± 7.76	
30	69.5 ± 11.77	76.33 ± 9.82	73 ± 9.70	

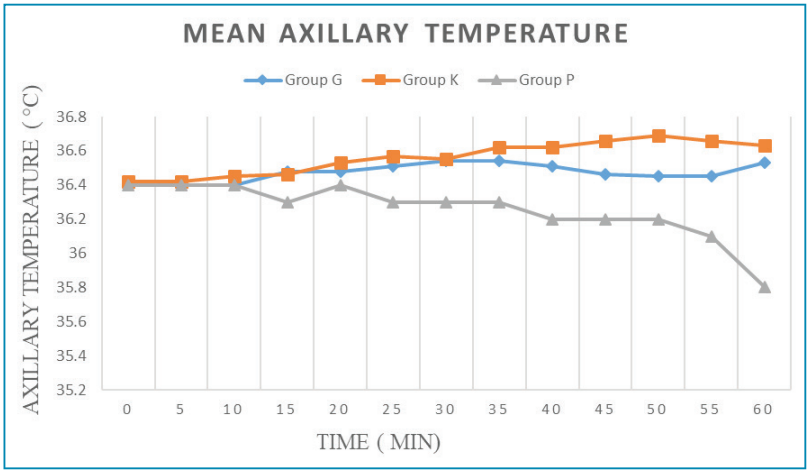

Fig. 6: Changes in peripheral temperature at various time points between the three groups.

Table 10: Mean axillary temperature ± SD in the three groups and statistical comparison				
Time (Min)	**Group G**	**Group K**	**Group P**	**P-value**
0	36.4 ± .00	36.42 ± .03	36.4 ± .05	0.0000001
5	36.4 ± .00	36.42 ± .03	36.4 ± .05	
10	36.4 ± .00	36.45 ± .05	36.4 ± .05	
15	36.48 ± .48	36.46 ± .18	36.3 ± .18	
20	36.48 ± .04	36.53 ± .05	36.4 ± .04	
25	36.51 ± .06	36.57 ± .06	36.3 ± .05	
30	36.54 ± .12	36.55 ± .09	36.3 ± .08	
35	36.54 ± .12	36.62 ± .14	36.3 ± .09	
40	36.51 ± .11	36.62 ±.14	36.2 ± .09	
45	36.46 ± .08	36.66 ± .16	36.2 ± .10	
50	36.45 ± .05	36.69 ± .17	36.2 ± .10	
55	36.45 ± .05	36.66 ± .15	36.1 ± .06	
60	36.53 ± .05	36.63 ± .11	35.8 ± .07	

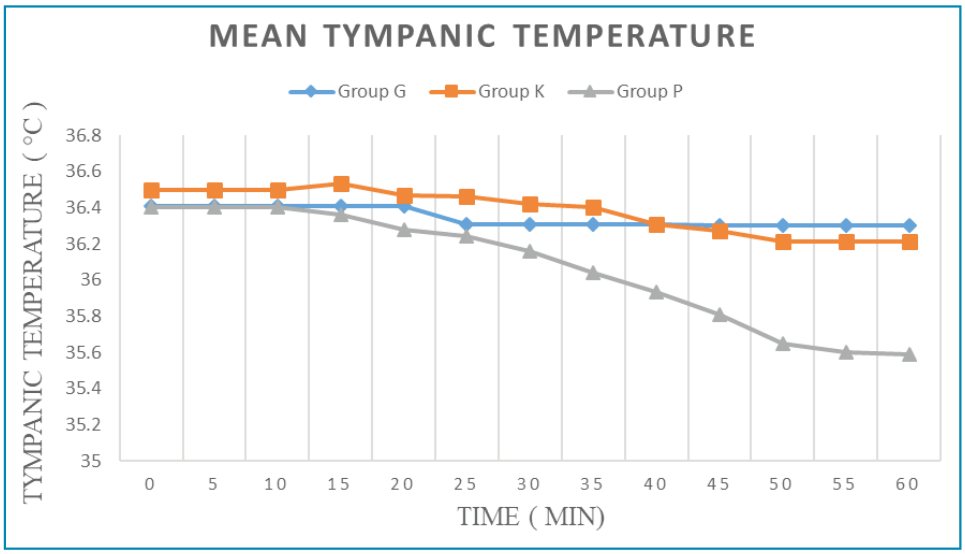

Fig. 7: Changes in tympanic temperature at various time points between the three groups.

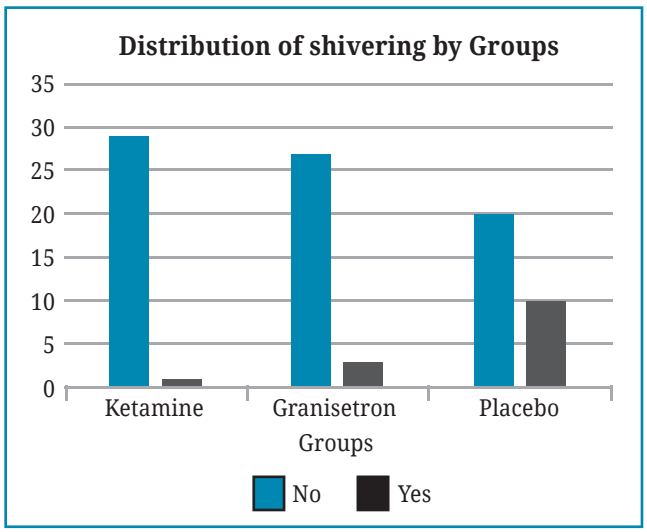

Fig. 3. 7: Distribution of shivering

Frequency of side-effects such as nausea, vomiting and headache was not significantly different in the three groups. Sedation was seen in 8 cases (26%) in Ketamine group, most of them were sedated to grade 2 and only 3 were of grade 3. No hallucinations were seen in any of the patients (Table 14).

DISCUSSION

Regional anesthesia is emerging as a safe and popular technique both in elective and emergency situations in modern anesthesia practice, however incidence of post-anesthesia shivering after regional anesthesia is very high upto 56.7%.[1,5] In this study, the incidence of shivering was 33% (10/30) in the control group

Table 11: Mean Tympanic temperature ± SD in the three groups and statistical comparison

Time (Min)	Group G	Group K	Group P	P-value
0	36.41 ± .03	36.5 ± .08	36.4 ± .00	
5	36.41 ± .03	36.5 ± .08	36.4 ± .00	
10	36.41 ± .03	36.5 ± .08	36.4 ± .00	
15	36.41 ± .03	36.5 ± .08	36.3 ± .05	
20	36.41 ± .03	36.4 ± .10	36.28 ± .04	
25	36.31 ± .03	36.4 ± .11	36.24 ± .04	
30	36.31 ± .03	36.4 ± .18	36.16 ± .04	0.0003
35	36.31 ± .03	36.4 ± .17	36.04 ± .05	
40	36.31 ± .03	36.3 ± .29	35.93 ± .11	
45	36.3 ± .00	36.2 ± .27	35.81 ± .03	
50	36.3 ± .00	36.2 ± .34	35.65 ± .08	
55	36.3 ± .00	36.2 ± .34	35.6 ± .19	
60	36.3 ± .00	36.21 ± .34	35.59 ± .17	

Table 12: Number of patients with different grades of shivering after 15 min of spinal anesthesia				
Shivering score	**Group G**	**Group K**	**Group P**	**P-value**
0	27	29	20	0.414
1	0	0	2	0.135
2	3	1	0	0.173
3	0	0	8	0.0003
4	0	0	0	

Table 13: Grades of shivering after 15 min of spinal anesthesia in groups G and K			
Shivering score	**Group G**	**Group K**	**P-value**
0	27	29	
1	0	0	
2	3	1	0.023
3	0	0	
4	0	0	

Table 14: Nausea, Sedation and Headache incidence of group				
	Group G (n=30)	**Group K (n=30)**	**Group P (n=30)**	**P value**
Nausea	0	1 (% 3.3)	0	0.367
Sedation	0	8 (% 26)	0	0.0003
Headache	0	1 (% 3.3)	0	0.367

which was significantly higher than the other two groups (Table 12).

Shivering causes increased metabolic activity and increased oxygen consumption up to 100%. It increases cardiac output, peripheral resistance, carbon dioxide production and lactic acidosis.[5,20] It also causes arterial hypoxia and has been shown to correlate with increased risk of myocardial ischemia. It increases intracranial and intraocular pressure. Moreover it interferes with ECG and oxygen saturation monitoring (pulse oximetry).[21–23]

Shivering is a response to hypothermia. Body temperature should normally be maintained within limits of 36.5–37.5 °C.[16] Factors like Age, level of sensory block, temperature of used local anesthetic, temperature of the operating room and infusion solution are risk factors for hypothermia in regional anesthesia.[1] For these reasons, in this study, patients over the age of 60 years were excluded from the study, the temperature of the operating room was maintained at 24°C, and infusions of cold crystalloid solutions were avoided.

A variety of physical and pharmacological methods have been tested in reducing peri-operative hypothermia and suppressing post-anesthetic shivering. Physical methods include radiant heaters, increasing ambient temperature, and space blankets. Pharmacological methods include meperidine, ketanserin, sufentanil, alfentanil, tramadol, clonidine etc.[8,9] However, none of these have received universal acceptance because of reported specific side-effects of these agents including hypotension, hypertension, sedation, respiratory depression, and nausea and vomiting.[8,9,24,25] The agents used for the treatment or prophylaxis of shivering during regional anesthesia should not cause nausea and vomiting or haemodynamic instability.

During regional anesthesia, granisetron, a 5-HT3 receptor antagonist, has been shown to be effective in the prevention of emetic symptoms at dose of 40 µg/kg IV.[17]

Serotonin (5-hydroxytryptamine), a biological amine found in the brain and spinal cord, has a role in neurotransmission.[26] Activation of nucleus raphe magus, where 5-HT acts as a neurotransmitter has inhibitory effect on shivering. Indeed, tramadol, which inhibits 5-HT reuptake, and ketanserin, a 5-HT2 antagonist, inhibit established post-anesthetic shivering.[9] All these observations suggest that the serotonergic system has a role in the control of post-anesthetic shivering.

Regional anesthesia produces vasodilatation, which facilitates core-to-peripheral redistribution of heat.[13] Ketamine, a competitive NMDA receptor antagonist has a role in thermoregulation at various levels. NMDA receptor modulates noradrenergic and serotoninergic neurons in locus coeruleus. It increases blood 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.[14] Thus, it appeared logical to use ketamine in patients who are at risk of hypothermia.

This prospective randomized control study was conducted to compare efficacy and safety of prophylactic low dose ketamine and granisetron for prevention of shivering during spinal anesthesia. A total of 90 patients undergoing different surgical procedures under spinal anesthesia were enrolled in this study. They were randomly divided into three groups with 30 in each and were similar with respect to age, weight, height, ASA physical status.

There was no significant difference among the 3 groups in relation to hemodynamic parameters. Hemodynamic parameters like heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were monitored every 5 minutes throughout intraoperative period.

Body temperature was monitored with a tympanic non-invasive thermosan thermometer and an axillary thermometer at the start of spinal anesthesia and intraoperatively. In our study the mean core temperature (Tympanic) decreased from baseline value after spinal anesthesia and the decline was seen in all three groups (Fig. 7 and Table 11). However, significant decrease in mean core temperature (tympanic) was seen in saline (placebo) groups as compared to ketamine and granisetron group (P = <0.05). This is expected because hypothermia during spinal anesthesia is common.[2,3] There are three principal reasons for hypothermia under spinal anesthesia. First, spinal anesthesia decreases hypothalamic threshold by 0.5°C, triggering vasoconstriction and shivering above level of the block.[2] Secondly, loss of thermoregulatory vasoconstriction below the level of the spinal block, leads to increased heat loss from body surfaces. Lastly, spinal anesthesia leads to an internal redistribution of heat from the core to the peripheral compartment.[4] The axillary body temperatures in group K were significantly higher than saline (placebo) groups (P <0.001) and granisetron group (P <0.05). This is because ketamine causes direct central sympathetic stimulation and inhibition of norepinephrine uptake into postganglionic sympathetic nerve endings, and may decrease core-to-peripheral redistribution of heat.[11] Similar results were also noted from studies done by Sagir *et al*[5] and Shakya *et al*.[19]

In Our study, 8 out of 30 (26.6%) patients in saline (Placebo) group experienced shivering at grade 3 and this was significantly higher than granisetron groups and ketamine group (P <0.001). Ten percent of patient (3/30) in granisetron and 3% of patient (1/30) in ketamine group experienced shivering at grade 02. Shivering was significantly higher in granisetron (G) group as compared to ketamine (K) group (P <0.05). The mechanism which leads to shivering after regional anesthesia is not very clear, but the probable mechanism could be decrease in core body temperature secondary to sympathetic block; peripheral vasodilation; increased cutaneous blood flow, which leads to increased heat loss through skin; cold temperature of operation theatre and rapid infusion of intravenous cold fluids.[27–29]

Many studies have demonstrated the usefulness of granisetron and ketamine in prevention of shivering.[5,15,19,30] Different doses of granisetron from 40 µg/kg to 3mg were used to prevent shivering in different studies.[5,30,31] In the study done by Sagir *et al*[5] after 15 min of spinal anesthesia, 55% of patients in control group, 15% in granisetron group, 0 in ketamine group had shivering. Number of patients with observable shivering was comparable with our study, 26% (8/30) in placebo group with p-value <0.05 and only 10% (3/30) in granisetron group with p-value >0.05. However, one patients in ketamine group had shivering of scale 02 (p > 0.05) which may be due to low dose of ketamine in our study.

Similarly, in study done by Shakya *et al*.[19] Shivering was observed in 42.50% of patients in saline group, 10% patients in ondansetron group and in only 2.5% patient in ketamine group, which is very similar to our study.

In the study done by Sajedi *et al* [30] shivering was observed in 27% patients in granisetron group which was lower than control group but higher than our study, 10 % in granisetron group. These authors conducted the study in patients who received general anesthesia and the difference may be the result of the differences between the mechanisms of shivering during general and regional anesthesia.

In the study of Sharma *et al*[32] ketamine, at dose 0.5mg/kg given intravenously (I.V), appeared

effective in the treatment of shivering after general and regional anesthesia but patients developed hallucinations and sedation. Because of this reason in this study, we used low dose of ketamine (0.25 mg/kg) to prevent shivering during spinal anesthesia.

In our study, sedation score was lower than 3 in most of the patients. However, sedation score was significantly higher in group K (26%) than the other groups (P <0.001). No hallucinations were seen in any of the patients (Table 14).

Zhou *et al*[33] conducted a meta-analysis of 16 trials including 1485 patients and found that ketamine reduced the incidence of post-anesthetic shivering compared to a placebo and no evident variability of the incidence of nausea and vomiting compared to a placebo. Hallucinations were more frequently observed in patients who received higher doses of ketamine. Findings of this meta- analysis support our study.

Similarly, Wason *et al*[34] did not observe major hemodynamic changes following use of ketamine for prevention of shivering in patients undergoing surgery under neuraxial block. However, sedation was significantly higher with ketamine as compared to other drugs used in their study. Results of this study are similar to our study in relation to incidence of shivering and adverse effects of ketamine.

Despite having few limitations, we obtained a result which was commensurate with various literatures that concluded low dose ketamine and granisetron to be effective in prevention of shivering during spinal anesthesia. But there were few studies which were incongruous with the results of our study.

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