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Research Article

Prospective, randomized, double blind, placebo controlled clinical study to different doses of ketamine for prevention of shivering during spinal anaesthesia

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ABSTRACT

Background: Ketamine has better effect than other drugs like pethidine, fentanyl, clonidine, tramadol, midazolam in prevention of shivering during anaesthesia and has a role in thermoregulation by different means. The objective of this study was to evaluate the safety, efficacy of Ketamine injection and to compare the different doses (0.25 mg/kg and 0.5 mg/kg) of inj. Ketamine in prevention of shivering in operative patients under spinal anaesthesia.
Methods: The present study was a prospective, randomized, double blinded and clinical study conducted in L.T.M.M.C & L.T.M.G.H, Mumbai, India during January 2012 to September 2013. 120 patients with American Society of Anesthesiologist (ASA) physical status of I or II, between the age of 18 – 65 years of either sex and height 150-170 cms were randomly selected and included in the study as per eligibility.
Results: The study suggests that prophylactic administration of injection Ketamine at doses of 0.25 mg/kg and 0.5 mg/kg was producing a significant antishivering effect but an incidence of sedation and hallucination was observed in the Ketamine 0.5 mg/kg receiving group throughout the perioperative period.
Conclusions: From this study we can conclude that prophylactic dose of Ketamine 0.25 mg/kg i.v. has lesser side effects comparison to Ketamine 0.5 mg/kg i.v. in prevention of shivering in patients, undergoing surgical procedure under spinal anaesthesia.

Keywords: Ketamine, Shivering, Perioperative, Shivering score, Spinal anaesthesia

INTRODUCTION

Perioperative hypothermia and shivering is among the unwanted, recurrent health issues in surgical patients undergoing both general and regional anaesthesia. Reports say the occurrence of shivering in patients recovering from general anesthesia to be between 5-65% whereas 40=60% in patients recovering from regional anesthesia.[1-3]

Although unintended hypothermia is may provide protection against ischemia, there are also several clinical reports which indicate multiple physiological derangements include coagulation abnormalities due to impaired platelet function, wound infection with delayed wound healing due to impaired immunoregulation etc. caused by hypothermia.[4] Hypothermia during neuraxial anaesthesia develops initially from core to peripheral redistribution of body heat. Redistribution of body heat during spinal or epidural anaesthesia typically decreases core temperature 0.5-1.0°C.[5]

Shivering is another convoluted response of hypothermia, and is defined as tremor of the face, jaw, head, trunk or extremities lasting longer than 15 seconds.[6] It causes augmented consumption of oxygen, arterial hypoxia and myocardial ischemia. It also raises intracranial and intraocular pressure. The other effects include increase in

cardiac output, peripheral resistance, production of carbon dioxide and lactic acidosis. Moreover it also interferes with ECG and oxygen saturation monitoring (pulse oximetry).[2,7]

Various non-pharmacological and pharmacological measures have been studied to control intraoperative shivering which include covering bared body parts with surgical drapes or blankets, airway heating and humidification, warming intravenous fluids and active cutaneous warming with insulator. In addition, a variety of medications are used which include drugs like Injection pethidine, fentanyl, clonidine, tramadol, midazolam.[4,8]

Recently ketamine has been reported with better results in prevention of shivering during anaesthesia. It is a competitive receptor antagonist of N-methyl-d-aspartic acid (NMDA) has a role in thermoregulation by different means.[8] Ketamine controls shivering by non-shivering thermogenesis either by the action on the hypothalamus or by the β-adrenergic effect of Norepinephrine.[9] It is used as antishivering agent in dose of 0.25-0.75 mg/kg i.v.[3,10]

Thus, the authors were designed this placebo controlled, randomized, double blinded, prospective study to evaluate the safety, efficacy of inj. Ketamine and to compare the different doses (0.25 mg/kg and 0.5 mg/kg) of inj. Ketamine in prevention of shivering in operative patients under spinal anaesthesia. It was also aimed to compare the adverse reactions, if any.

METHODS

The present study was a prospective, randomized, double blinded and clinical study conducted in L.T.M.M.C & L.T.M.G.H, Mumbai, India during January 2012 to September 2013. After approval of the institutional medical ethics committee 120 patients with American Society of Anesthesiologist (ASA) physical status of I or II, between the age of 18-65 years of either sex and height 150-170 cms were included in the study. Written informed consent was obtained from all patients to be included in the study. Patient unwilling for consent, with thyroid disorder, severe cardiopulmonary disease, requiring transfusion of blood and blood products, endoscopic urological procedures, pregnancy, BMI >30 kg/m^2, contraindication for central neuraxial blockade, Coaugulopathy, H/O any allergy to local anaesthetic were excluded from the study.

Eligible 120 patients were distributed into 3 groups, each parallel group containing 40 patients each. The patients scheduled to undergo infraumbilical surgical procedures including hernioplasty, appendicectomy, gynaecological procedures, urological procedures and orthopedics procedures lasting upto 150 minutes under spinal anaesthesia were enrolled in the study. After intrathecal injection, 4 ml of one of the study drug was given i.v. bolus. Group K was given Inj Ketamine 0.25 mg/kg i.v.; group O was treated with Inj Ketamine 0.5 mg /kg i.v. and Group P was the placebo or control group.

A complete preoperative assessment was carried out in all patients. Patients selected were randomized in three groups using chit block method allotting equal number of patients in each group.[11] A syringe with 4 ml of study drug was prepared by an anaesthesiologist, who was not involved in administration of subarchanoid block or recording the outcome. Temperature of operation theatre was checked and maintained at 22-26 ^{0}C. Anaesthetic drugs and equipments were kept ready before starting procedure.

After confirmation of starvation status and consent, patient was taken in operation theatre. Monitors like electrocardiogram, pulse-oximeter and NIBP was attached. Core temperature was recorded with the help of nasopharyngeal temperature probe. Patients with baseline temperature <35 ^{0}C or >38 ^{0}C were excluded from study. The base line parameters such as heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), SpO_2 and core temperature were recorded. An IV line was secured and patient was preloaded with IV fluid (Ringer's Lactate) at the rate of 10 ml/kg/hr. The preloading IV fluids and the IV infusions, kept at room temperature were used during operation.

Procedure was explained to the patient. Under all aseptic precautions, subarachnoid block was given in sitting position, in L3-L4 space, by midline approach with Quincke's spinal needle no. 25. After confirming free and clear flow of CSF and negative aspiration of blood, Inj. Bupivacaine 0.5% (Heavy) 3.5 cc was injected. Supine position was given. A standard double layered bed sheet was used to cover the chest and upper limbs of all patients.

Just 5 min after the intrathecal injection, 4 ml of one of the study drugs was given as IV bolus. The level of sensory block with help of pinprick test was assessed every 5 minutes intervals. The presence of shivering was observed. Patients with inadequate sensory level <T8 fifteen minutes after administration of sub archanoid block or severe pain intraoperatively were excluded from the study.

Parameters including core temperature with the help of nasopharyngeal temperature probe, heart rate, blood pressure, SpO_2, electrocardiography monitoring, shivering score, Sedation score were noted and monitored every 15 min till end of surgery and every 30 minutes for 2 hours in postoperative period:

Shivering was graded using a scale similar to that validated by Tsai and Chu.[2]

Grade 0: no shivering;

Grade 1: piloerection or peripheral vasoconstriction but no visible shivering;
Grade 2: muscular activity in only one muscle group;
Grade 3: muscular activity in more than one muscle group but not generalized;
Grade 4: shivering involving the whole body.

If 15 minutes after spinal anaesthesia and concomitant administration of a prophylactic dose of one of the study drugs, the patients shivered to at least grade 3, shivering was considered significant and prophylaxis as ineffective. Injection Tramadol 1 mg/kg IV slowly was given as a rescue drug.

The degree of 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. All patients were given oxygen at rate of 6 ltr/min with Hadson's mask in intraoperative period and monitored every 15 min till the end of surgery and every 30 min till 2 hours.

Statistical data

Data was expressed as mean ± standard deviation or median. Demographic data and complications were analyzed using Pearson's chi square test and hemodynamic variables; core temperature, shivering score and sedation score were analyzed using Kruskal-Wallis one way analysis of variance on ranks test. P values <0.05 were considered as significant.

RESULTS

Prospective, randomized, double blind, placebo controlled clinical study, designed to evaluate and compare the efficacy of ketamine at doses of (0.25 mg/kg i.v.) and (0.5 mg/kg i.v.) for prevention of shivering during spinal anaesthesia. 120 patients of either sex (18-65 yrs) were randomly allocated in 3 groups (Group O: Inj Ketamine 0.5 mg/kg i.v.; Group K: Inj Ketamine 0.25 mg/kg i.v. and Group P: placebo or saline group) each parallel groups containing 40 patients each.

Table 1 shows demographic data including age, weight, height and body mass index. Demographic characteristics were compared using Kruskal-Wallis one way analysis of variance on ranks test. All the three groups were comparable, in view of demographic parameters, including age, weight, height and body mass index. Statistically, there was no significant difference.

Sex ratio, sensory level, ASA class are given in Table 2. These characteristics were compared using Pearson chi square test. All the three groups were comparable. Statistically, there was no statistically significant difference.

All the three groups were compared for perioperative core temperature at different time intervals. Baseline core temperatures of all the three groups were comparable. The groups showed highest temperature initially. Difference was statistically significant in all the three groups, at all time intervals except at baseline core temperature.

Table 1: Demographic data of the patients.

Study parameter		Group O	Group K	Group P	p value
Age (years)	Mean	39.40	39.53	39.48	0.975
	Std.Dev.	8.26	9.69	7.80	
	Median	39.00	39.00	38.00	
	IQR	13.00	14.50	12.50	
Weight (kgs)	Mean	59.58	61.08	59.70	0.777
	Std.Dev.	9.01	9.29	7.94	
	Median	58.00	60.00	60.00	
	IQR	13.50	14.50	11.50	
Height (cm)	Mean	155.18	156.15	156.60	0.373
	Std.Dev.	4.86	4.87	5.29	
	Median	154	154	155	
	IQR	4.50	6.00	6.50	
BMI (kg/m^2)	Mean	24.58	24.85	24.21	0.918
	Std.Dev.	2.62	2.54	2.06	
	Median	24.0	25.0	24.5	
	IQR	4.85	3.75	2.95	

P<0.05-significant

Table 2: Sex, Sensory blockage, ASA class of the patients.

Study Parameters		Group O	Group K	Group P	p value
Sex(M/F)	M	21 (52.5%)	18 (45%)	28 (70%)	0.068
	F	19 (47.5%)	22 (55%)	12 (30%)	
Sensory level (T_6/T_7)	T_6	28 (70%)	23 (57.5%)	32 (80%)	0.092
	T_7	12 (30%)	17 (42.5%)	8 (20%)	
ASA class (I/II)	I	25 (62.5%)	31 (77.5%)	28 (70%)	0.343
	II	15 (37.5%)	9 (22.5%)	12 (30%)	

P<0.05-significant

Table 3: Perioperative core temperature.

Study group	Study parameters	Mean	Std.Dev.	Median	IQR	P value
Group O	Core temp BL	36.70	0.46	36.80	0.75	
Group K		36.77	0.38	37.00	0.60	0.800[NS]
Group P		36.69	0.58	37.00	1.25	
Group O	15 mins	36.58	0.48	36.75	0.90	
Group K		36.56	0.35	36.60	0.40	0.006
Group P		36.25	0.57	36.30	0.90	
Group O	30 mins	36.49	0.55	36.75	1.10	
Group K		36.42	0.43	36.55	0.45	0.000
Group P		36.09	0.50	36.25	0.90	
Group O	45 mins	36.50	0.46	36.65	1.00	
Group K		36.40	0.36	36.55	0.55	0.040
Group P		36.18	0.51	36.10	0.50	
Group O	60 mins	36.43	0.54	36.60	0.80	
Group K		36.55	0.32	36.55	0.35	0.006
Group P		36.31	0.33	36.40	0.45	
Group O	75 mins	36.36	0.54	36.40	0.70	
Group K		36.59	0.24	36.60	0.40	0.001
Group P		36.33	0.28	36.30	0.30	
Group O	90 mins	36.37	0.56	36.40	1.30	
Group K		36.71	0.19	36.80	0.30	0.039
Group P		36.48	0.36	36.35	0.60	

p<0.05-significant; NS-Statistically not significant

All the three groups were compared for pulse rate perioperatively, at different time intervals. Baseline pulse rates of all the three groups were comparable. Highest pulse rate was shown after 15 and 30 minutes. Difference was statistically significant in all the three groups, at all-time intervals except at baseline pulse rate.

Baseline mean arterial pressures of all the three groups were comparable and presented in Table 5. All the three groups were compared for mean arterial pressure perioperatively, at different time intervals. Difference was statistically significant in all the three groups, at all-time intervals except at baseline mean arterial pressure.

Table 6 presents perioperative shivering score and all the three groups were compared at different time intervals. Difference was statistically significant in all the three groups, at all-time intervals. Group p showed highest score after 30 minutes which gradually decreased with increase of time.

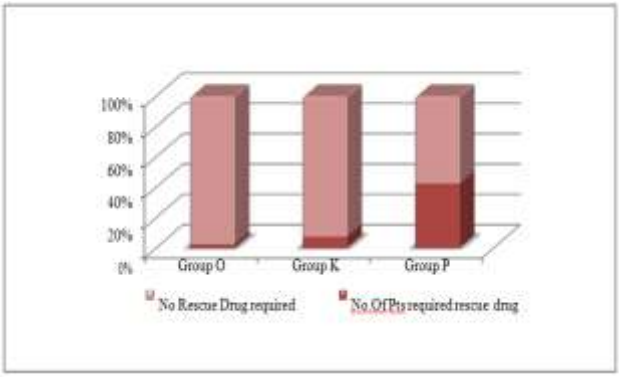

Figure 1: Number of patients required rescue drug.

Table 4: Perioperative pulse rate.

Study group	Study parameters	Mean	Std. Dev.	Median	IQR	P value
Group O	PR BL	69.43	6.78	68.50	9.00	0.080[NS]
Group K		72.63	8.05	71.50	10.00	
Group P		72.88	7.89	75.00	13.50	
Group O	15 mins	82.58	8.11	80.00	12.50	0.000
Group K		81.03	8.17	85.00	13.00	
Group P		68.10	8.25	66.00	6.00	
Group O	30 mins	80.65	4.61	82.00	8.50	0.000
Group K		81.13	7.78	82.00	12.00	
Group P		68.95	9.98	68.00	5.00	
Group O	45 mins	79.68	5.54	79.00	11.00	0.000
Group K		79.25	6.89	81.50	10.00	
Group P		71.13	7.45	70.00	12.00	
Group O	60 mins	78.68	6.08	78.50	11.00	0.000
Group K		79.08	6.12	80.00	10.00	
Group P		73.05	9.48	70.00	14.00	
Group O	75 mins	76.55	6.52	76.00	10.00	0.001
Group K		77.41	5.31	78.00	9.00	
Group P		71.83	9.06	69.00	13.50	
Group O	90 mins	76.28	8.09	72.00	11.00	0.001
Group K		77.81	2.18	76.00	4.00	
Group P		71.69	8.69	70.00	9.50	

p<0.05-significant; NS-Statistically not significant

Table 5: Perioperative mean arterial pressure.

Study Group	Study Parameter	Mean	Std.Dev.	Median	IQR	P value
Group O		96.10	8.30	96.00	10.00	
Group K	MAP BL	95.10	7.55	93.00	8.00	0.626[NS]
Group P		95.18	8.56	96.00	15.00	
Group O		100.90	9.21	98.00	17.00	
Group K	15 mins	94.05	8.74	95.00	10.00	0.000
Group P		81.38	6.79	82.00	6.50	
Group O		102.40	16.69	101.00	7.00	
Group K	30 mins	93.18	8.74	98.00	11.00	0.000
Group P		80.15	6.30	81.00	12.00	
Group O		97.75	7.41	98.50	9.00	
Group K	45 mins	91.45	8.12	93.00	6.00	0.000
Group P		82.25	7.66	82.00	9.00	
Group O		96.05	6.35	96.00	7.00	
Group K	60 mins	91.05	6.97	93.00	5.00	0.000
Group P		83.00	6.84	83.00	7.50	
Group O		95.40	6.50	95.00	10.00	
Group K	75 mins	91.44	6.56	93.00	11.00	0.000
Group P		85.13	6.00	84.50	8.00	
Group O		95.56	5.33	98.50	11.00	
Group K	90 mins	85.67	3.43	84.00	8.00	0.000
Group P		87.07	6.34	86.00	7.50	

p<0.05-significant; NS-Statistically not significant

Table 6: Perioperative shivering score.

Study Gr	Study Parameter	Mean	Std. Dev.	Median	IQR	P value
Group O	15 mins	0.10	0.38	0.00	0.00	
Group K		0.53	0.60	0.00	1.00	0.000
Group P		1.55	0.93	2.00	1.00	
Group O	30 mins	0.28	0.72	0.00	0.00	
Group K		0.58	0.78	0.00	1.00	0.000
Group P		2.13	0.72	2.00	0.00	
Group O	45 mins	0.25	0.49	0.00	0.00	
Group K		0.78	0.83	1.00	1.00	0.000
Group P		1.63	0.67	2.00	1.00	
Group O	60 mins	0.58	0.50	1.00	1.00	
Group K		0.33	0.47	0.00	1.00	0.000
Group P		1.15	0.36	1.00	0.00	
Group O	75 mins	0.55	0.50	1.00	1.00	
Group K		0.05	0.22	0.00	0.00	0.000
Group P		1.10	0.50	1.00	0.00	
Group O	90 mins	0.61	0.50	1.00	1.00	
Group K		0.05	0.21	0.00	0.00	0.000
Group P		0.83	0.38	1.00	0.00	

p<0.05-significant

Table 7: Perioperative sedation score.

Study group	Study parameters	Mean	Std. Dev.	Median	IQR	P value
Group O		2.85	0.43	3.00	0.00	
Group K	15 mins	1.73	0.55	2.00	1.00	0.000
Group P		1.10	0.30	1.00	0.00	
Group O		2.70	0.52	3.00	1.00	
Group K	30 mins	1.35	0.53	1.00	1.00	0.000
Group P		1.35	0.58	1.00	1.00	
Group O		2.08	0.42	2.00	0.00	
Group K	45 mins	1.18	0.50	1.00	0.00	0.000
Group P		1.55	0.88	1.00	1.50	
Group O		1.98	0.28	2.00	0.00	
Group K	60 mins	1.13	0.33	1.00	0.00	0.000
Group P		1.58	0.78	1.00	1.00	
Group O		1.83	0.38	2.00	0.00	
Group K	75 mins	1.08	0.27	1.00	0.00	0.000
Group P		1.63	0.87	1.00	1.50	
Group O		1.72	0.46	2.00	1.00	
Group K	90 mins	1.05	0.21	1.00	0.00	0.000
Group P		1.44	0.73	1.00	1.00	

p<0.05-significant

Figure 1 shows number of patients who required rescue drug (i.e. Tramadol 1 mg/kg) when patient shivered to Grade 3 or more than 3. Group P had maximum no. of patients who required Rescue Drug as compared to Group O and Group K. Difference was statistically significant.(p<0.05).

All the three groups were compared for Sedation score perioperatively, at different time intervals which was tabulated in Table 7. Difference was statistically significant in all the three groups, at all time intervals.

All the three groups were compared for core temperature postoperatively and presented in Table 8. The values of the groups after 30 minutes are statistically significant. Postoperative core temperatures, except at 30 mins, of all the three groups were comparable.

All the three groups were compared for pulse rate postoperatively, at different time intervals. Difference was statistically significant in all the three groups, at all time intervals.

Table 8: Postoperative core temperature.

Study Gr	Study Parameter	Mean	Std.Dev.	Median	IQR	P value
Group O	PO Core temp 0 min	36.43	0.40	36.50	0.80	
Group K		36.46	0.23	36.50	0.40	0.538^{NS}
Group P		36.48	0.37	36.50	0.40	
Group O	30 mins	36.32	0.42	36.30	0.75	
Group K		36.35	0.21	36.40	0.20	0.001
Group P		36.51	0.34	36.50	0.30	
Group O	60 mins	36.39	0.32	36.30	0.30	
Group K		36.43	0.27	36.40	0.50	0.338^{NS}
Group P		36.45	0.35	36.50	0.60	
Group O	90 mins	36.39	0.27	36.30	0.30	
Group K		36.46	0.34	36.60	0.70	0.377^{NS}
Group P		36.47	0.44	36.50	1.00	
Group O	PO Core temp 120 mins	36.38	0.33	36.30	0.70	
Group K		36.41	0.35	36.40	0.45	0.914^{NS}
Group P		36.42	0.42	36.20	0.90	

p<0.05-significant; NS-Statistically not significant

Table 9: Postoperative pulse rate.

Study Group	Study Parameter	Mean	Std.Dev.	Median	IQR	P value
Group O	0 mins	75.55	7.31	72.00	12.00	
Group K		73.88	5.81	70.00	10.00	0.041
Group P		70.60	8.18	72.00	18.00	
Group O	30 mins	76.30	7.04	73.50	7.50	
Group K		75.20	4.78	74.00	4.50	0.039
Group P		71.55	7.18	74.00	10.00	
Group O	60 mins	74.70	6.70	72.00	11.00	
Group K		74.93	2.89	75.00	5.00	0.000
Group P		70.88	6.70	70.00	10.50	
Group O	90 mins	74.00	7.16	71.00	9.00	
Group K		75.08	3.74	76.00	6.50	0.000
Group P		69.78	6.29	70.00	5.00	
Group O	120 mins	73.30	7.74	70.00	11.00	
Group K		74.45	5.47	71.00	10.00	0.006
Group P		70.05	6.77	70.00	5.00	

p<0.05-significant

Table 11 showed shivering score postoperatively, at different time intervals. Highest score was found in case of Group P in 0 minutes followed by 30 minutes. Difference was statistically significant in all the three groups, at all time intervals.

Sedation score postoperatively is given in Table 12 at different time intervals. Group O with 0 minute followed by 30 minutes showed higher results in comparison to other groups. Difference was statistically significant in all the three groups, at all time intervals except at 120 mins.

Table 13 shows perioperative complications among all the three groups. In Group O, 20% patients had hallucinations and that of Group K only 2.5% patients had hallucinations. Difference was statistically significant. Nausea and vomiting was seen only in Group P, incidence being 10%.There was no incidence of bradycardia, hypotension and hypertension noted in any group.

All the three groups were compared for Mean Arterial pressure postoperatively, at different time intervals and presented in Table 10. Group o showed highest value after 30 minutes. Difference was statistically significant in all the three groups, at all time intervals.

Table 10: Postoperative mean arterial pressure.

Study group	Study Parameters	Mean	Std.Dev.	Median	IQR	P value
Group O	PO MAP 0 mins	95.80	7.12	97.00	8.00	0.000
Group K		90.40	5.91	93.00	10.00	
Group P		85.13	7.44	83.00	5.50	
Group O	30 mins	96.28	9.34	96.00	14.50	0.000
Group K		90.65	6.70	90.50	9.50	
Group P		85.95	7.58	82.00	9.00	
Group O	60 mins	95.18	9.16	99.00	16.00	0.000
Group K		91.68	8.85	95.50	16.00	
Group P		86.73	7.75	83.50	11.00	
Group O	90 mins	91.93	5.83	93.00	8.00	0.000
Group K		91.50	6.76	93.00	7.00	
Group P		86.60	5.90	85.00	11.50	
Group O	PO MAP 120 mins	93.53	8.81	96.50	20.00	0.003
Group K		91.78	6.47	93.00	5.00	
Group P		87.38	6.04	84.00	9.50	

p<0.05-significant

Table 11: Postoperative shivering score.

Study group	Study parameters	Mean	Std.Dev.	Median	IQR	P value
Group O	PO Shivering Sc 0 mins	0.48	0.51	0.00	1.00	0.000
Group K		0.93	0.57	1.00	0.00	
Group P		1.60	0.63	2.00	1.00	
Group O	30 mins	0.28	0.51	0.00	0.50	0.000
Group K		0.65	0.62	1.00	1.00	
Group P		1.33	0.62	1.00	1.00	
Group O	60 mins	0.28	0.64	0.00	0.00	0.000
Group K		0.00	0.00	0.00	0.00	
Group P		0.88	0.40	1.00	0.00	
Group O	90 mins	0.35	0.70	0.00	0.00	0.000
Group K		0.03	0.16	0.00	0.00	
Group P		0.48	0.51	0.00	1.00	
Group O	PO Shivering Sc 120 mins	0.35	0.70	0.00	0.00	0.006
Group K		0.03	0.16	0.00	0.00	
Group P		0.30	0.46	0.00	1.00	

(p<0.05-significant)

Table 12: Postoperative sedation score.

Study group	Study parameters	Mean	Std.Dev.	Median	IQR	P value
Group O	PO Sedation sc 0 mins	2.18	0.50	2.00	0.00	0.000
Group K		1.28	0.45	1.00	1.00	
Group P		1.53	0.72	1.00	1.00	
Group O	30 mins	1.98	0.28	2.00	0.00	0.000
Group K		1.13	0.33	1.00	0.00	
Group P		1.48	0.72	1.00	1.00	
Group O	60 mins	1.78	0.42	2.00	0.00	0.000
Group K		1.05	0.22	1.00	0.00	
Group P		1.23	0.42	1.00	0.00	
Group O	90 mins	1.25	0.44	1.00	0.50	0.013
Group K		1.03	0.16	1.00	0.00	
Group P		1.13	0.33	1.00	0.00	
Group O	PO Sedation sc 120 mins	1.00	0.00	1.00	0.00	1.000
Group K		1.00	0.00	1.00	0.00	
Group P		1.00	0.00	1.00	0.00	

(p<0.05-significant)

Table 13: Perioperative complications.

Complications	Group O (n=40)	Group K (n=40)	Group P (n=40)	P value
Nausea and vomiting	0/40 (0%)	0/40 (0%)	4/40 (10%)	0.016
Hallucinations	8/40 (20%)	1/40 (2.5%)	0/40 (0%)	0.001
Bradycardia	0/40 (0%)	0/40 (0%)	0/40 (0%)	NS
Hypotension/Hypertension	0/40 (0%)	0/40 (0%)	0/40 (0%)	NS

Data was analysed by using Pearson chi square test. NS-Statistically not significant.

DISCUSSION

Shivering can be distressing to the patient and has been cited as one of the primary causes of discomfort during the perioperative period. The most significant physiological consequence is an increased oxygen demand to six times that may lead to hypoxia and death.[3,12,13] Mild hypothermia is accompanied with compromised immunity, delayed wound healing, coagulopathy, increased risk in allergenic blood transfusions, delayed post anaesthetic recovery, prolonged hospitalistion, discomfort, and morbid myocardial outcomes secondary to sympathetic nervous system stimulation.[14] It is thus imperative that monitoring temperature in patients undergoing general anaesthesia longer than 30 min and major operations under neuraxial anaesthesia.[14]

Various pharmacological agents have been evaluated for their efficacy in preventing and treating shivering, however, a "gold standard" drug treatment has not been defined.[12] Previously several number of pharmacological agents are used in preventing and treating shivering but these drugs had a wide-range of unpredictable side effects, including respiratory depression, hypotension, sedation, itching, nausea and vomiting.[7] Recently ketamine is proved as an good drug in prevent shivering during anaesthesia without causing cardiovascular or respiratory depression.[15] It controls shivering by non-shivering thermogenesis either by the action on the hypothalamus or by the β-adrenergic effect of Norepinephrine by decreasing core to peripheral redistribution of heat.[16]

Generally the dose of ketamine for induction and maintenance of general anesthesia is 1-2 mg/kg but that dose is associated with deleterious side effects. Previous studies proved that ketamine at a doses of 0.25-0.75 mg/kg was considered as an effective antishivering agent during perioperative period with reduced side effects.16 Hence the present study is aimed to compare the efficacy between two doses of ketamine 0.25 mg/kg and 0.5 mg/kg (i.v. bolus) for prevention of shivering during spinal anaesthesia in peri-operative period.

In the present study fall in core temperature was observed in all the groups, as compared to baseline values, but it is less in patients receiving Inj Ketamine. These observations are in accordance with the previous studies done by Kose et al and Sagir et al.[17,18]

The efficacy of ketamine as an antishivering agent was also proved in the studies conducted by Shakya et al.[2] He found that fall in temperature was more significant in saline and ondansetron group than in ketamine (0.25mg/kg) group at all time intervals. In the study done by Kinoshita et al proved that low-dose ketamine administration may confer thermoprotection during spinal anesthesia sedated by propofol.[19] This relative preservation of core temperature in the ketamine groups may be attributed to the sympathetic stimulation and vasoconstrictive effects of the drug.[7,16]

In our study perioperative median shivering score was higher in control group and they are required with rescue drug as compared to patients receiving ketamine. These results are similar to the studies carried out by Shakya et al.[2] In our study, we found that, the incidence of shivering in the control group is (42.5%) which is lower (as compared to 55%); and in the ketamine (0.5 mg/kg) group it was 2.5% which is higher to 0% as in the comparative study conducted by Sagir et al. He compared the efficacy of Ketamine (0.5 mg/kg), Ketamine (0.25 mg/kg) plus Granisetron (1.5 mg), Granisetron (3 mg) and saline in patients undergoing urological surgeries In our study it is also found that the Inj Ketamine 0.5 mg/kg group had lower incidence of shivering (2.5%) as compared to 18% in the studies done by Ahmed A. et al.[20]

From the results of our study, we found that incidence of significant shivering in control group was 42.5% and in Inj Ketamine 0.5 mg/kg group is 2.5% that was comparably lower than the study conducted by Wason et al proving the efficacy of ketamine as prophylactic agent during perioperative period.[21]

In a study conducted by Mirza Koeshardiandi et al concluded that ketamine 0.25 mg/kg i.v. is effective in lowering shivering after spinal anaesthesia in cesarean section either before or after the baby is born, with same effectiveness as pethidine 0.5 mg/kg and the same outcome were also supported by Dal and his colleagues in a double blind study using normal saline, 0.5 mg/kg Ketamine and 20 mg Pethidine prophylactically in preventing post operative shivering in patients who underwent general anaesthesia.[22,7] Results clearly showed

that prophylactic dose 0.5 mg/kg of Ketamine and 20 mg of Pethidine were significantly effective and equal in controlling postoperative shivering than the placebo without side effects.

In this study perioperative pulse rate, mean arterial blood pressure was observed to be higher in patients receiving Ketamine as compared to placebo group but did not observed any incidence of tachycardia, bradycardia, hypotension or hypertension. These results are similar with the previous studies of Wason et al.[21] This relative preservation of hemodynamics in the ketamine groups may be attributed to the sympathetic stimulation and vasoconstrictive effects of the drug.

Perioperative median sedation score were observed more with Ketamine 0.5 mg/kg i.v. along with a common side effect of hallucination compared to 0.25 mg/kg received group. These effects are significantly similar to the previous studies of Kose et al, Safavi et al and Abdelrahman et al.[10,8,23] But other side effects like nystagmus, feeling like walking in space, delirium was not observed in patients after receiving Ketamine 0.75 mg/kg which was observed in the previous study done by Kose et al.[24]

The findings of our study suggest that prophylactic administration of injection Ketamine at doses of 0.25 mg/kg and 0.5 mg/kg was producing a significant antishivering effect but an incidence of sedation and hallucination was observed in the Ketamine 0.5 mg/kg receiving group throughout the perioperative period. In conclusion, prophylactic dose of Ketamine 0.25 mg/kg i.v. is preferred over ketamine 0.5 mg/kg i.v. for prevention of shivering in patients, undergoing surgical procedure under spinal anaesthesia, with lesser side effects.

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