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CLINICAL EFFICACY OF INTRAVENOUS BUTORPHANOL, GRANISETRON AND KETAMINE FOR PREVENTION OF POST SPINAL SHIVERING -A COMPARATIVE EVALUATION

[1]*Prof. Gupta Kumkum MD, DA, [2]Dr. Sharma Raaghav MBBS, [3]Dr. Singh Ivesh MD, [4]Dr. Zuberi Azka MD, [5]Prof. Gupta Prashant K. MD, DMRE, FICRI, FIAMS, [6]Dr. Bansal Manoranjan MD.

Department of Anesthesiology and Critical Care, Department of Radio-Diagnosis and Interventional Imaging, Subharti Medical College, Swami Vivekanand University, NH-58 By Pass Road, Meerut-UP, India.

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***Corresponding Author**
Prof. Gupta Kumkum
Department of Anesthesiology and Critical Care, Department of Radio-Diagnosis and Interventional Imaging, Subharti Medical College, Swami Vivekanand University, NH-58 By Pass Road, Meerut-UP, India.

ABSTRACT

Background and aim- Subarachnoid block is safe anesthetic technique but associated with variable hypotension, bradycardia and shivering. Shivering is a physiological response to core hypothermia in an attempt to raise the metabolic heat production. The present study was aimed to compare the clinical efficacy of intravenous butorphanol, granisetron and ketamine for prevention of post spinal shivering. ***Patients and Method-*** One hundred and twenty adult patients of American Society of Anaesthesiologists (ASA) physical status I and II of both genders, scheduled for surgical procedures under subarachnoid block and met the selection criteria, were randomized into four equal groups of 30 patients each, to receive either normal saline (Group NS), butorphanol 1 mg (Group B), granisetron 2 mg (Group G) or ketamine 50 mg (Group K) intravenously after institution of subarachnoid block. The incidence and grades of shivering were noted as a primary outcome. Secondary outcomes were changes in hemodynamics, sedation or any adverse effects of study drugs. ***Results-*** Post spinal shivering was observed in 42% patients of Group NS, 10% patients of Group B, 23% patient of Group G and 3% patients of Group K. The duration of sensory and motor block was prolonged in patients of Group B with statistically significant difference. Incidences of hypotension and bradycardia were comparable. All patients showed sedation score of 2 or 3 but respiratory depression was not observed in any

patients. ***Conclusion-*** Intravenous ketamine 50 mg was more effective for prevention of post-spinal shivering with hemodynamic stability and sedation.

KEYWORDS: Butorphanol, Granisetron, Ketamine, Spinal anesthesia, Shivering.

INTODUCTION

Subarachnoid block is reliable and safe regional anesthetic technique but leads to variable fall in blood pressure primarily due to peripheral vasodilation, bradycardia and shivering. Shivering is a thermoregulatory response to core hypothermia to raise the metabolic heat production with increased oxygen consumption and carbon dioxide production, hence increased cardiac work. The incidence of post-spinal shivering may be 40 to 70%. The aetiology for post-spinal shivering may be redistribution of heat from the core to the periphery, cold environment of operating rooms and rapid infusion of cold fluids. Shivering causes discomfort to patients and also interferes the monitoring of vital parameters.[1, 2, 3]

Local anesthetics impaired the centrally mediated thermoregulation by altering the afferent thermal inputs. The neurotransmitter pathways are complex and involved opioids, α-2 adrenergic, serotonergic and anticholinergic receptors. Therefore, drugs acting on these receptors could be utilized for the prophylaxis of shivering. The pharmacological intervention with clonidine, ketamine, doxapram, opioids and 5HT3 receptor antagonist resets the shivering threshold to a lower level thereby decreasing the episodes of shivering.[4]

Physical use of equipment to maintain normal body temperature is effective but expensive while using pharmacological method is cost effective. In country like India, restriction on drug licensing of opioids and unavailability of many other drugs, compound the problem further.

Butorphanol is agonist- antagonist opioid analgesic and acts on central mono-aminergic pathways to inhibit the neuronal uptake of noradrenaline/serotonin.[5,6] Granisetron is a 5-HT3 antagonist and influence both heat production and heat loss.[7,8] Ketamine is a competitive NMDA receptor antagonist and acts by modulating the thermoregulation either by non-shivering thermogenesis action on the hypothalamus or by the β-adrenergic effects of norepinephrine, but it may cause drowsiness, delirium and hallucinations.[9]

Many studies were carried out to evaluate the antishivering effects of various drugs but none compared them together. The present study was aimed to compare the clinical efficacy of

intravenous butorphanol, granisetron and ketamine for prevention of shivering in patients undergoing lower abdominal surgeries under subarachnoid block.

PATIENTS AND METHOD

After approval of Institutional Ethical Committee and written informed consent, 120 adult patients of American Society of Anaesthesiologists (ASA) physical status I and II of both genders, aged between 18-68 years, weighing 45-85 kg, scheduled for elective lower abdominal surgeries under subarachnoid block, were enrolled for the present prospective randomized double blind control study.

Patients with history of severe cardiac or pulmonary disease, uncontrolled hypertension, morbid obesity, neurologic or psychological disease, hepatic or renal dysfunction, thyroid disease or metabolic disorders, dearranged coagulation profile and deformity of spinal column were excluded from the study. Patients requiring intraoperative blood transfusion, acute infections or fever (temperature >38^{o}C), known hypersensitivity to study drugs, infection at the site of lumbar puncture, refusal to the technique and uncooperative patient were also excluded from study.

Patients were randomly allocated to receive normal saline (Group NS, n=30), butorphanol 1 mg (Group B, n= 30), granisetron 2 mg (Group G, n=30), or ketamine 50 mg (Group K, n=30) using a computer generated table of random numbers. The treatment drugs were prepared, diluted to a volume of 10 mL and labelled by another resident anaesthesiologist who was not further involved for data recording to ensure blindness of study.

All enrolled patients were admitted prior to day of operation and were premedicated with alprazolam 0.5 mg and ranitidine 150 mg on the night before surgery.

After arrival in the operation theatre, monitoring for heart rate, electrocardiogram, pulse-oximetry, non-invasive arterial blood pressure and axillary temperature were commenced and noted. They were infused lactated Ringer solution at rate of 10 mL/kg over 15 minutes, before initiation of subarachnoid block and no means of active rewarming was used.

The subarachnoid block was initiated at L2-L3 or L3-L4 intervertebral space with 3.5 ml of 0.5% hyperbaric bupivacaine (17.5 mg) under all aseptic precautions and patient was placed in supine position with 10^{0} Trendelenburg tilt to achieve the sensory block up to T10 dermatome. All patients were given midazolam 2 mg, followed by study drug solution

according to group allocation and supplemental oxygen was given at rate of 4 mL/min via face mask.

The sensory and motor block characteristics were assessed till required surgical anaesthesia was achieved. The segmental level of sensory blockade to pin prick was assessed bilaterally along the mid clavicular line. The onset of sensory blockade was defined as the time from intrathecal injection to the occurrence of sensory block at dermatome level T10. The maximal level of sensory block was also noted. The duration of sensory blockade was defined as the time interval from intrathecal administration of local anesthetic to S2 segment regression.

The motor blockade of the lower extremities was evaluated by Modified Bromage Scale (0=able to move hip, knee and ankle; 1=unable to move hip, able to move knee and ankle; 2=unable to move hip and knee, able to move ankle; and 3=unable to move hip, knee and ankle). The onset of motor block was defined as the time interval from intrathecal injection to the absence of toes activity. The duration of motor block was defined as the time interval from the onset of motor blockade to the time of the achievement of modified Bromage Scale zero (0).

The hemodynamic parameters of systemic arterial pressure, heart rate, ECG and pulse-oximetry were monitored at 5 minute intervals till end of surgery and then in recovery room. For the present study, hypotension was defined as blood pressure less than 20% of baseline and was managed by increasing the intravenous infusion rate of lactated Ringer solution and, if required, additionally with intravenous bolus of mephenteramine 6 mg. Bradycardia was defined as heart rate less than 60 b/m and was treated with intravenous atropine in titrated dosages.

Assessment of Shivering

Intraoperatively the shivering was recorded at 5-minute interval up to 60 minutes of surgery, using a scale validated by Wrench:[10]

Grade 0: No shivering,

Grade 1: Piloerection but no visible muscular activity,

Grade 2: Visible muscular activity confined to one muscle group,

Grade 3: Visible muscular activity in more than one muscle group but not generalized,

Grade 4: Gross muscular activity (Shivering) involving the whole body.

The prophylaxis for shivering was regarded as ineffective if the patient exhibits grade-3 shivering any time during the study. Patients, who developed grade 3 or more of shivering were treated with tramadol (50 mg intravenously) with ondansetron 4 mg.

Level of sedation was evaluated by Ramsay Sedation Scale at every 30 minutes considering the time of giving the study drug as zero. Ramsey Sedation Scale (1=patient was anxious, agitated or restless; 2=patient was co-operative, oriented and tranquil; 3=patient responded to commands only; 4=patient exhibited a brisk response to light glabellar tap or loud auditory stimulus; 5=patient exhibited a sluggish response to light glabellar tap or loud auditory stimulus; and 6=patient exhibited no response.

The subarachnoid block characteristics, hemodynamic parameters, shivering with its onset time and grade, time of disappearance, level of sedation and any other intraoperative adverse events were recorded for statistical analysis.

Side effects of nausea, vomiting or respiratory depression were noted and managed according to clinical protocol. Vomiting, if occurred was treated with metoclopramide 10 mg intravenously. At the end of surgery, the patients were shifted to the recovery room and monitored for any changes in vital signs, sedation and hallucinations.

Study population size and Statistical analysis

The sample size was calculated with standard computer programs which computed that minimum 25-27 patients per group should be included to observe the reduced incidence of shivering from 50% to 15% with the α-error of 0.05 and a β-error of 0.2 with 95% confidence level. Assuming a 5% drop out rate, the final sample size was set at 120 patients for better validation of results.

The results are presented in a tabulated manner as Mean ± SD and were analysed using Stat Graphics Centurion, version 16.2 (Stat point Technologies INC, Warrenton, Virginia). The chi-square test was used to compare the difference of demographic data. The statistical significance in mean difference was calculated using repeated-measures ANOVA followed by Bonferroni's post hoc test. A p value of <0.05 was considered to indicate statistical significance.

RESULT

The present study was successfully completed by 120 enrolled patients without exclusion during the follow-up period. The demographic data of age, body mass index, gender and ASA was comparable. [Table-1].

Table: 1 Demographic data

	Group NS	Group B	Group G	Group K	P-value
Age(years)	39.4 ±9.8	38.9±10.4	38.3±11.8	40.1±10.9	0.93
Weight (Kg)	68.8±7.5	67.5±9.2	69.9±8.7	66.9±9.4	0.54
BMI(Kg/m^2)	27.4±2.7	27.6±2.7	28.1±2.7	26.2±3.6	0.09
Gender(M/F)	12/18	17/13	12/18	16/14	0.43
ASA I/II	29/1	26/4	24/6	24/6	0.20

Data are presented as Mean ± SD and absolute numbers.

Shivering

Shivering at different time intervals was recorded and compared in patients of all the four groups. No shivering was observed in any patient at baseline or just after establishing the subarachnoid block. Only 3% patient suffered from shivering at 5 min interval in Group NS and none in other 3 groups. A high percentage of patients (23%) had shivering in Group NS, followed by 10% in Group B, 20% in Group G and only 3% in Group K at 15 min interval. [Table-2].

Table 2 Number of patients with different grades of shivering in four groups

	Grades 0/1/2/3/4			
	Group NS (n=30)	**Group B (n=30)**	**Group G (n=30)**	**Group K (n=30)**
Baseline	0/0/0/0/0	0/0/0/0/0	0/0/0/0/0	0/0/0/0/0
5 min after SAB	0/1/0/0/0	0/0/0/0/0	0/0/0/0/0	0/0/0/0/0
15 min after SAB	0/4/3/0/0	0/3/0/0/0	0/4/2/0/0	0/1/0/0/0
30 min after SAB	0/2/0/0/0	-	0/0/1/0/0	-
45 min after SAB	0/0/3/0/0	-	-	-
60 min after SAB	-	-	-	-
Total	**13 (42%)**	**3 (10%)**	**7 (23%)**	**1 (3%)**

Data are presented as numbers and percentage of patients. Group NS received normal saline; Group B received butorphanol 1mg; Group G received granisetron 2 mg; Group K received ketamine 50 mg. SAB- Subarachnoid block.

Subarachnoid block Characteristics

The mean onset time of complete sensory block and maximal sensory dermatome level were comparable among the four groups. The mean duration of sensory block was 208.17±23.69.

min, 270.10±12.64 min, 226.77 ± 11.16 min and 260.77±11.16 min in patients of Groups NS, B, G and K respectively with statistically significant difference (P = 0.021). [Table-3].

The mean onset time of complete motor block was comparable. The duration of motor block for Group NS, B, G and K was 178.37 ± 16.1 min, 211.20 ± 22.91 min, 189.53 ± 17.8 min and 207.15 ± 18.72 respectively with statistically significant difference (P= 0.042).

Table 3 Subarachnoid block characteristics

	Group NS (n=30)	Group B (n=30)	Group G (n=30)	Group K (n=30)	P value
Onset of Sensory block	4.27±1.14	4.23±1.19	4.13±.86	4.23±1.10	0.968
Maximum sensory level	T6-7	T7-8	T6-7	T6-7	
Duration of sensory block	208.17±23.69	270.10±12.64	226.77±11.16	260.77±11.16	0.021*
Onset of motor block	5.17±.69	5.03±1.09	5.53±1.04	5.30±.75	0.186
Duration of motor block	178.37±16.1	211.2± 22.91	189.53±17.8	207.15±18.72	0.042*

*Data are presented as Mean ± SD and median; *P value < 0.05 is statistically significant. Group NS received normal saline; Group B received butorphanol 1mg; Group G received granisetron 2 mg; Group K received ketamine 50 mg.*

Hemodynamic Profile

The mean heart rate of all patients were comparable before commencement of subarachnoid blockade (SAB). After 5 min of SAB, the mean heart rate in patients of all the groups increased to 89.03 ± 16.13, 84.77 ± 9.65, 89.27 ± 16.01 and 88.17 ± 15.21 beats/min in patients of Groups NS, B, G and K respectively. Thereafter, there had been a gradual decline in heart rate in patients of all groups except in patients of Group K. The variation in the mean heart rate among the groups was not statistically significant. [Table-4].

Table: 4 Comparison of heart rate (beats/min)

Time interval	Group NS	Group B	Group G	Group K	P-value
Base line	75.23±11.51	79.30±7.94	75.23±11.51	75.23±11.51	0.362
After SAB	89.03±16.13	84.77±9.65	89.27±16.01	89.27±16.01	0.567
5 min	92.93±15.58	90.37±13.22	93.50±15.04	93.17±15.40	0.839
15 min	82.97±14.96	82.60±13.78	84.27±14.53	83.43±14.90	0.974
30 min	71.40±7.98	71.73±8.34	73.43±9.39	71.63±8.28	0.782
45min	70.43±7.98	70.27±9.54	72.10±9.23	70.43±7.98	0.829
60 min	71.03±7.84	70.00±8.13	72.93±9.22	71.27±8.15	0.595
Post- Operative	71.27±7.55	72.03±9.89	73.60±10.14	73.60±10.14	0.715

Data are presented as Mean ± SD; P value >0.05is not statistically significant.

The mean arterial pressure among the four groups at base line was comparable but it differed significantly (p <0.05) among the groups up to 30 minutes after institution of SAB. Thereafter it showed increasing trend as the time interval increases with statistically significant difference among the groups (p<0.05). [Table-5].

Table 5 Comparison of mean arterial pressure (mm Hg)

Time interval	Group NS	Group B	Group G	Group K	P-value
Base line	78.03±6.82	76.23±8.24	78.27±8.25	78.03±6.82	0.705
After SAB	77.33±6.34	75.87±7.99	79.57±8.36	77.93±6.74	0.284
5 min	78.40±6.59	74.47±8.15	79.87±7.40	79.07±6.78	0.024*
15 min	79.00±18.46	73.00±8.89	80.43±8.85	89.07±6.66	0.000**
30 min	78.97±7.21	71.43±7.18	79.73±7.26	79.47±7.17	0.000**
45min	76.17±5.92	73.83±6.13	76.67±6.11	76.67±6.11	0.220
60 min	77.90±7.00	75.97±5.30	78.17±6.92	78.17±6.92	0.506
Post-Operative	76.97±6.45	77.90±6.38	77.90±6.38	77.90±6.38	0.923

*Data are presented as Mean ± SD; *P value < 0.05 is statistically significant; ** P value < 0.001 is statistically highly significant.*

SIDE-EFFECTS

Hypotension was observed in patients of all the four groups. Nine patients in Group NS had hypotension followed by 7 patients in Group G, five patients in Group B while only 1 patient of Group K, managed by increasing the infusion rate of lactated Ringer. No vasopressor medication was required. Bradycardia was observed in 10 patients of Group B, 5 patients of Group NS while only in 2 patients of Groups G, managed with incremental doses of atropine sulphate.

Nausea and vomiting was observed in 6 patients of Group NS, followed by Group B and Group K with one patient each, while no patient suffered from episode of nausea and vomiting in Group G. All patients showed sedation score of 2 or 3 and were comfortable. Respiratory depression did not occur in any patient of the study groups. [Table-6].

Table 6 Number of patients experiencing various side effects

	Group NS	Group B	Group G	Group K	P-value
Hypotension	9(30%)	5(16.66%)	7(23.33%)	1(3.33%)	0.051
Bradycardia	5(16.66%)	10(33.33%)	2(6.66%)	0	0.14
Nausea and vomiting	6(20%)	1(3.33%)	0	1(3.33%)	0.08
Pruritus	0	0	0	0	1
Respiratory depression	0	0	0	0	1

Data are presented as numbers and percentage of patients.

DISCUSSION

Shivering is thermoregulatory response to core hypothermia along with skin-vasomotor activity and non-shivering thermogenesis as principal defences against hypothermia. Shivering is due to internal redistribution of heat from core to peripheral compartment, heat loss to the environment because of vasodilation of lower limbs vessels, impairment of centrally mediated thermoregulatory control, exposure to cold operating room environment and intravenous fluids. It increases the metabolic activity, oxygen consumption and carbon dioxide production hence lactic acidosis and arterial hypoxia.[11,12] Due to shivering and thermal discomfort, the quality of patient recovery suffers. Therefore prevention of shivering is more important than its treatment.

The neurotransmitter pathways involved in shivering are complex and include opioids, α-2 adrenergic, serotonergic and anticholinergic receptors. Therefore, drugs acting on these receptors could be utilized for the prophylaxis as well as for its treatment.[13, 14]

In regional anesthesia, shivering develops in up to 56.7% of patients. In the present study, the incidence of shivering was in 42% patients of normal saline group, 23% patients of granisetron group, 10% patients of butorphanol group while only 3% patients of ketamine group.

Ketamine modulates the noradrenergic and serotoninergic neurons in the locus coeruleus and in the dorsal horn of the spinal cord to provide the transmission of the ascending nociceptive stimuli. It causes sympathetic stimulus and peripheral vasoconstriction thus preserve body temperature.[15,16] Butorphanol acts as agonist at opioid k-receptors and antagonist at opioid μ- receptors and modulate the central mono-aminergic pathways to inhibit the neuronal uptake of noradrenaline/serotonin and encourages hydroxytriptamine secretion to reset the body temperature centre.[5, 17] Granisetron is the specific inhibitor of the 5-HT3 receptors and causes generalized thermoregulatory inhibition at the level of the hypothalamus by a central mechanism.[18]

O Sagir *et al* reported that ketamine 0.5 mg/kg was better than intravenous granisetron or combination of ketamine plus granisetron for preventing the shivering related to regional anaesthesia.[19] Wason *et al* compared the antishivering efficacy of prophylactic ketamine, clonidine and tramadol and concluded that patients of ketamine group suffered lowest grade of shivering.[20] Their results were similar to present study which showed that prophylactic

intravenous administration of ketamine 50 mg was more effective (3% of patients) than butorphanol (10% of patients) and granisetron (23% of patients) during spinal anaesthesia for prevention of shivering.

Dal *et al* studied the anti-shivering effects of ketamine, pethidine and normal saline. They observed that the patients receiving normal saline suffered grade 2 shivering, which was more when compared to patients of ketamine group.[21] Bansal *et al* compared the clonidine, butorphanol and tramadol to control post spinal shivering and showed the superiority of butorphanol (17%) over tramadol (27%) and clonidine (29%) which was comparable to the present study in terms of butorphanol.[22]

Mohammad SS *et al* did a clinical trial for efficacy of granisetron for prevention of shivering during caesarean delivery under spinal anesthesia and concluded that granisetron was an effective way to prevent shivering, nausea and vomiting during spinal anesthesia with no effect on APAGAR score of new born.[23]

In the present study, there was significant difference of mean arterial pressure and heart rates among the groups. Bansal *et al* observed the propensity of fall in blood pressure in all the three groups receiving clonidine, tramadol and butorphanol. O Sagir *et al* reported the fewer incidences of hypotension with granisetron which was similar with present study. In the present study no vasopressor medication was required to manage the hypotension which may be due to preloading of all patients before initializing the subarachnoid block.

The incidence of nausea and vomiting was maximum with the normal saline group (6/30) while no patient complained of nausea and vomiting in granisetron group. Ketamine and butorphanol causes sedation of scale 2or 3 which can be beneficial for comfort of the patient, and cardiorespiratory stability. They prevents recall of unpleasant events during the surgery. Ketamine is known to cause psychosomatic effects, but in the present study, none of the patients complained of any such effects which may be due to use of midazolam in premedication.

CONCLUSION

The present study concluded that intravenous ketamine 50 mg was clinically more advantageous and efficient for prevention of post spinal shivering. It prevents intraoperative

hemodynamic alterations and prevents recall of unpleasant events along with arousable sedation.

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