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Original Article

Anaesthesia Section

Effects of Intravenous Ketamine, Butorphanol and Fentanyl for the Management of Intraoperative Shivering under Spinal Anaesthesia- A Randomised Clinical Trial

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ABSTRACT

Introduction: Neuraxial block can cause intraoperative shivering. Though, so many drugs have been studied for treatment of shivering, none has been found ideal. N-methyl-D-aspartate (NMDA) antagonist like ketamine, k-opioid receptor agonist butorphanol and μ receptors agonist fentanyl have shown antishivering effect but each one has its own demerits.

Aim: To examine the efficacy of ketamine, butorphanol, and fentanyl in suppressing shivering under spinal anaesthesia in elective lower abdomen and lower limb surgery.

Materials and Methods: The double-blind, randomised trial was conducted between June 2011 to September 2013. A total of 90 patients, posted for surgery under spinal anaesthesia, were randomly allocated into three groups of 30 each. After giving spinal anaesthesia, patients who developed shivering (grade 3 or more), lasting for more than 3 minutes, the study drugs were administered. Patients in Group I received ketamine (0.5 mg/kg), Group II received butorphanol (0.02 mg/kg) and Group III received fentanyl (1 μg/kg), intravenously. Time taken to control shivering, sedation and any side-effects nausea and vomiting were assessed. The dose was given over 60 seconds and the time duration for the complete disappearance of shivering was noted (after the drug administration) at 2 min, 5 min, 10 min, 20 min, and 30 min. The sedation score was determined after 10 minutes of administering drug. Comparison of the observations among different groups was done and statistically analysed using Fisher-exact test, ANOVA, Chi-square test.

Results: Shivering control time was much shorter in Group II (3.6±1.20 min) than in Group I (3.867±1.676 min), but significantly longer in Group III (5.467±2.047 min). Mean age of Group I, II and III was 37.6, 34, 36.7 respectively. Reappearance of shivering was substantially more common in Group III (20%) than in Groups-I (0%) and II (0%).

Conclusion: Ketamine, buterophanol and fentanyl are equally effective for controlling shivering at 10 minutes after the administrating of study drugs but butorphanol is faster acting, followed by ketamine and then fentanyl to control of shivering.

Keywords: Control, Reappearance, Sedation

INTRODUCTION

A fasciculation that may be easily detected and lasts for more than 15 seconds is considered to be shivering. Incidence of shivering under sub arachnoid block is varied from 41-60% [1,2]. The vasoconstriction and shivering threshold are significantly lowered by neuraxial blockade [3]. The primary cause of hypothermia in neuraxial anaesthesia is peripheral rather than central inhibition of thermoregulatory control. Besides, shivering is uncomfortable to the patient, and it also leads to an increased consumption of oxygen (by 100-600%) above baseline, also produces more carbon dioxide, tachycardia and hypertension, raised intracranial pressure and lactic acidosis [4,5].

To prevent shivering, both pharmacological drugs and non pharmacological methods are used. The non pharmacological methods are radiant heater, humidifier, warming mattresses and blankets, blood and intravenous fluid warmer etc. When non pharmacological methods fail, then drugs are used to prevent shivering. Many drugs have been used for the prevention and treatment of perioperative shivering, like pethidine, meperidine, nalbuphine, tramadol, physostigmine, and ondensetron [6-11]. Meperidine possesses special antishivering properties. A μ receptor agonists, fentanyl (25μg) may be more efficacious than a placebo in treating postanaesthesia shivering [12]. Butorphanol's ability to prevent shivering is mediated via k-opioid receptors [13]. Ketamine, a competitive NMDA receptor antagonist, has a variety of degrees of roles in thermoregulation. Ketamine likely regulates shivering by either modulating hypothalamic thermogenesis or via the beta adrenergic impact of norepinephrine. Ketamine affects the activity of nucleus-mediated raphe, which acts on receptors centrally.

There are studies which compared the effectiveness of ketamine to other drugs like clonidine, tramadol as antishivering agent, fentanyl to pethidine, morphine and butorphanol to tramadol, clonidine [14-16]. But there are none which compared ketamine, butorphanol and fentanyl together. Hence, the aim of the study was to evaluate and compare the efficacy and safety of the study drugs on shivering, in patients who underwent lower abdomen and lower limb surgeries. Primary outcome measures were the time taken to control the shivering after using administration of the study drugs. Secondary outcome measures were any side-effects (nausea and vomiting, sedation).

MATERIALS AND METHODS

The double-blind, randomised trial was conducted between June 2011 to September 2013 in the Anaesthesiology and Critical Care Department, SCB Medical College, Cuttack, Odisha. The Institutional Ethical Committee approved the study (letter no. IEC/IRB NO:833/14.6.2011), and informed written consents were obtained.

Inclusion criteria: Patient's aged 18-55 years under American Society (ASA) category 1/2 scheduled for elective surgery under spinal anaesthesia were included in the study.

Exclusion criteria: Hypo and hyperthyroidsm, morbid obesity BMI ≥40 Kg/m^2, compromised cardiorespiratory function, ASA grade >2,

significant systemic illness, patients on Monoamine oxidase Inhibitors (MAOIs), tricyclic antidepressant, allergic reaction to drug, patients who had fever, pregnancy, have had history of seizure before, conditions contraindication for neuroxial blockade, patient taking opioid analgesics before surgery.

Sample size calculation: Considering a clinically significant reduction of shivering incidence from 42-10% [17] in intervention groups, an alpha of 0.05 and a beta of 0.8 was chosen and calculated using below mentioned formula, that 28 patients would be required in each study arm.

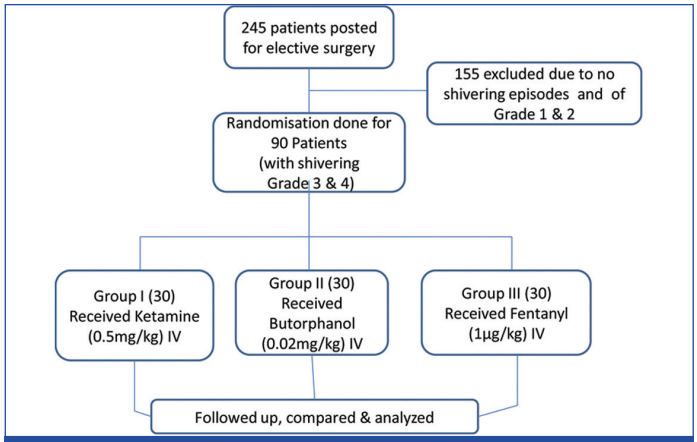
n=(Zα/2+Zβ)2*(p1(1-p1)+p2(1-p2))/(p1-p2)2

Out of 245 patients 90 patients were randomly (Computerised Randamosation) allocated into 3 groups with 30 patients in each group [Table/Fig-1]:

Group I: (Ketamine) Patients were given ketamine i.v. (0.5 mg/kg)

Group II: (Butorphanol) Patients were given butorphanol i.v. (0.02 mg/kg)

Group III: (Fentanyl) Patients were given fentanyl i.v. (1 µg/kg)



[Table/Fig-1]: CONSORT flowchart.

Study Procedure

The patients planned for operations were kept overnight fasting after preoperative evaluation. Warm Ringer lactate (8-10 mL/kg) was preloaded to patients in the operating room. Baseline vitals were collected. According per procedure, spinal anaesthesia was provided. The procedure was initiated after the required level of sensory and motor block had been reached. The operating room temperature was kept between 22°C and 28°C, with a relative humidity of around 60%. Thermistor was used to record the temperature of the patients. The temperature probe was fixed over the course of the axillary artery and the arm was then abducted to measure the axillary temperature. Attending anaesthesiologists decided whether to give i.v. fluids and ephedrine for hypotension. During the procedure and in the recovery area, a face mask supplied an additional 4 L/min of oxygen. Vitals were documented when the patient started to shiver, and the severity of it was determined using a scale same to that validated by Crossley AW and Mahajan RP [18].

0. Shivering is not present,
1. There is no palpable shivering but there is piloerection or peripheral vasoconstriction
2. Only one muscle group is actively contracting
3. More than one muscle group is contracting but there is no widespread trembling
4. Full-body shivering

The sedation score following drug administration was noted as below. The sedation score was determined after 10 minutes of administering drug. Sedation was assessed on a five point scale. Sedation score [19]: Sedation was classified as- 0: alert; 1: arouses to voice; 2: arouses with gentle tactile stimulus; 3: arouses with vigorous tactile stimulus; 4: lack of responsiveness.

Any patient with nausea and vomiting >2 was treated with ondansetron 4 mg i.v. After giving spinal anaesthesia, shivering was developed (grade 3 or more), lasting for more than 3 minutes. One consultant opened the sealed envelope and prepared the drugs and handed over to the consultant who administered the drug (blinded to the drugs). The observer was also blinded to the drugs. Calculated dose (ketamine i.v 0.5 mg/kg, butorphanol i.v. 0.02 mg/kg, fentanyl i.v. 1 µg/kg) was diluted in 10 mL of distilled water and given to the patient as per randomisation. The dose was given over 60 seconds and the time duration for the complete disappearance of shivering was noted (after the drug administration) at 2 min, 5 min, 10 min, 20 min, and 30 min. Other vitals such as temperature, pulse, Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP), and SpO_2 were also measured. Any adverse effects that occurred after administering the study drug were also recorded and treated if necessary. If shivering did not stop after 15 minutes of receiving the study drug, the patient was actively warmed using a radiant heat warmer. In case, shivering recurred (15 minutes after the initial reaction), it was noticed and treated by vigorously warming the patient and repeating the same dosage of the study drug in the same group.

STATISTICAL ANALYSIS

Comparison of the observation among different groups was done and statistically analysed using Fishers-exact test, ANOVA, Chi-square test. All the analysis was done under the guidance of a statistician using GraphPad Instant Software. The p-value <0.05 was considered statistically significant.

RESULTS

Age, sex, weight, and operation length were statistically similar between the groups [Table/Fig-2]. As shown in [Table/Fig-3], the vital parameters were similar among three groups.

Groups	Age (years) (mean±SD)	p-value	Female/Male	p-value	Weight (Kg) (mean±SD)	p-value	Duration of surgery (Hours) (mean±SD)	p-value
I (Ketamine)	37.6±9.51	0.272	16/14	0.873	59.0±7.7	0.094	1.7±0.6	0.779
II (Butorphanol)	34±8.1		18/12		63.0±7.7		1.6±0.5	
III (Fentanyl)	36.7±9.14		17/13		62.5±7.6		1.659±0.549	

[Table/Fig-2]: Basic characteristics.

Vitals parameters (just before giving spinal anaesthesia)	Group I (mean±SD)	Group II (mean±SD)	Group III (mean±SD)	p-value
Temp (^{0}F)	98.6±0.51	98.6±0.52	98.563±0.564	0.947
Pulse/min	66.67±6.477	68.5±9.53	65.9±9.83	0.499
SBP (mm Hg)	117.7±6.721	119.0±8.27	115.5±7.825	0.205
DBP (mm Hg)	72.067±3.731	73.9±5.92	70.37±6.498	0.051
SpO_2 (%)	99.33±0.661	99.2±0.7	99.2±0.71	0.702

[Table/Fig-3]: Comparison of basal vital parameters just before giving spinal anaesthesia.

As shown in [Table/Fig-4], incidence of shivering were same in all three groups, severity was maximum in Group II and least in Group III. The vitals parameter was statistically similar in all three groups [Table/Fig-5].

Grade of shivering*	Group I n (%)	Group II n (%)	Group III n (%)	p-value
1/2	0	0	0	0.70
3	20 (66.7)	19 (63.3)	22 (73.3)	
4	10 (33.3)	11 (36.7)	8 (26.7)	

[Table/Fig-4]: Comparison of initial shivering grade (Before administration of study drugs).
*This study includes shivering of grade 3 and 4 only (as described in methodology)

Vital at shivering	Group I (mean±SD)	Group II (mean±SD)	Group III (mean±SD)	p-value
Temp (°F)	95.6±0.52	96.0±0.6	95.5±0.51	0.1006
Pulse/min	69.2±5.97	71.2±7.99	68.3±7.97	0.3012
SBP (mm Hg)	115±7.54	117±7.74	113±7.45	0.1299
DBP (mm Hg)	70.17±5.989	72.0±5.3	69.33± 7.01	0.2326
SpO_2 (%)	99.1±0.76	99.0±0.70	99.1±0.73	0.8294

[Table/Fig-5]: Mean vitals at time of shivering (Just before administrating the drugs).

As shown in [Table/Fig-6], at two minutes, shivering stopped in eight patients in Group I, nine in II and five in III and Group III showed the highest grade of severity. Reappearance shivering was substantially seen in fentanyl group. The time taken to complete control of shivering was lowest in Group II (3.6±1.2 min) and highest in Group III (5.467±2.047 min) [Table/Fig-7].

Time interval	Grade	Group I	Group II	Group III	p-value
2 min	0	8	9	5	I vs II=0.955 II vs III=0.411 III vs I=0.524
	3	16	15	16	
	4	6	6	9	
5 min	0	22	27	10	
	3	8	3	14	
	4	0	0	6	
10 min	0	30	30	30	
	3	0	0	0	
	4	0	0	0	
20 min	0	30	30	24	
	3	0	0	6	
	4	0	0	0	
30 min	0	30	30	26	
	3	0	0	3	
	4	0	0	1	

[Table/Fig-6]: Comparison of shivering grade among the groups at different time periods (in mins). 0 means shivering stopped.
p-value is not calculated for 5-30 min as, 80% of cells have an expected count less than 5

Mean time	Group I (Mean±SD)	Group II (Mean±SD)	Group III (Mean±SD)	p-value
Taken for complete control of shivering (Minutes)	3.867±1.676	3.6±1.2	5.467±2.047	I vs II=0.4809 II vs III=0.001 III vs I=0.0016

[Table/Fig-7]: Time taken to control shivering.

As shown in [Table/Fig-8], nausea and vomiting was seen in five patients in Group I and eight in Group II and three in Group III. The appearance of nausea and vomiting was significantly higher in Group II. Only three patients in Group I showed hallucination, whereas no patient in Group II and Group III showed hallucination. When compared to group fentanyl, ketamine and butorphanol group had more patients with sedation scores. (1 and 2) no such incidences in 3 and 4 (sedation score).

Side-effects	Group I n (%)	Group II n (%)	Group III n (%)
Nausea and vomiting	5 (16.7)	8 (26.7)	3 (10)
Sedation (at 10 minutes after drug administration)			
0	13 (43.3)	17 (56.6)	24 (80)
1	14 (46.6)	6 (20)	3 (10)
2	3 (10)	7 (23.3)	3 (10)
Hallucination	3 (10%)	0	0

[Table/Fig-8]: Side-effects of drugs administration.

DISCUSSION

Neuraxial block for lower abdomen and lower limb surgeries is popular technique. Shivering is a side-effect of neuraxial block estimated to affect 41-60% of patients [1,2]. Comparison of ketamine, butorphanol and fentanyl was done for control of shivering in regard to speed of action, effectiveness, reappearance and associated side-effects. These three agents together have not been compared in single study so far. Ketamine, a competitive NMDA receptor antagonist, has a variety of degrees of roles in thermoregulation [20]. Ketamine likely regulates shivering by either modulating hypothalamic thermogenesis or via the beta adrenergic impact of norepinephrine. Ketamine affects the activity of nucleus-mediated raphe, which acts on receptors centrally. Antishivering effects of butorphanols through kappa receptors. Fentanyl may potentially have antishivering effects through altering the activity of nucleus mediated raphe, which acts centrally on the μ receptors. Butorphanol controlled shivering significantly faster than ketamine and fentanyl.

Bansal P and Jain G concluded that Butorphanol was more effective in suppressing shivering than tramadol, and clonidine and time taken to terminate rigors was 3.5±1.0 minutes for butorphanol which was similar to the present study finding (3.6±01.2 min) [16]. Manne VS and Gondi SR found that fentanyl was more effective than butorphenol for control of shivering in spinal anaesthesia and it took less time to control shivering which was in contrast to present study [21]. This may be due to use of higher dose (1.7 mcg/kg) instead of 1 mcg/kg in their trial. Sadeh SS et al., found that ketamine showed better effect on shivering after spinal anaesthesia as compared to nalbuphine in patients undergoing elective surgery under spinal anaesthesia and time taken to terminate rigors was 3.77±1.3 minutes for ketamine which was similar to this study finding (3.86±01.6 min) [22]. Wason R et al., showed that ketamine improves the haemodynamic profile by its sympathomimetic effects [14]. Ketamine also provides adequate sedation for the patient which increases patient comfort during surgery and maintains cardiorespiratory stability, which was similar to the present study. Manne VS and Gondi SR also showed that sedation is more with both butorphanol and fentanyl which required supplemental oxygen therapy [21]. According to them butorphanol produced more nausea and vomiting compared to fentanyl similar to this study. As there was no literature available comparing these three specific drugs for treatment of shivering, further studies may be done to validate the present study finding.

Limitation(s)

This study was conducted at a single centre and the findings cannot be generalised.

CONCLUSION(S)

Although ketamine, buterophanol and fentanyl are equally effective for controlling shivering at 10 minutes but the butorphanol is faster acting followed by ketamine and then fentanyl. Fentanyl has slowest onset of action and higher rate of reappearance of shivering as compared to ketamine and butorphanol. Although side-effects like nausea and vomiting were marginally seen in ketamine and butorphanol group but few required antiemetic. When compared to group fentanyl, ketamine and butorphanol group had more patients with greater sedation scores.

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