

Control of Shivering with Prophylactic Ketamine During Subarachnoid Block: A Placebo-Controlled Randomised Double-Blind Study

Zoengmawia¹, Lalnunmawii Sailo²

ABSTRACT

Introduction: Shivering is a common and challenging side effect of anaesthesia and may result in different degrees of perioperative hypothermia. Hence, the aim of the study was to compare the efficacy of ketamine to prevent shivering during subarachnoid block inpatient undergoing elective surgery.

Material and Methods: We conducted a prospective randomized, double-blind placebo-controlled trial with total of 90 ASA I and II patients of either sex between the ages of 18 – 60 years undergoing elective infra-umbilical surgery under subarachnoid blocks. Random allocation of patients was done into Group1: ketamine at dose of 0.5 mg /kg (n=30), Group2: ketamine at dose of 0.25 mg /kg (n=30), Group3: saline (n=30).

Results: The study groups were comparable at the baseline. After spinal anaesthesia and concomitant administration of the study drug, shivering was observed only in 10% of patient with score 1 in Group 1 and Group 2. Whereas in placebo group 50% patients suffered different degrees of shivering and required treatment ($p < 0.05$). After drug injection % of patient had higher sedation score (3 or 2) which was significantly higher in Group 1 (3%) than Groups 2 and 3 (0%) ($P = 0.002$). Only 3.3% patients of group1 experienced hallucination and rest of the patients in any group had no hallucination (P value = 0.045)

Conclusion: Ketamine at a dose of 0.5 mg /kg had similar effects as that of ketamine at dose of 0.25 mg /kg when compared to placebo group. However, ketamine at dose of 0.5 mg /kg caused higher effects of sedation and hallucination.

Keywords- Shivering, Ketamine, Subarachnoid Blocks, Elective Infra-Umbilical Surgery

INTRODUCTION

Humans have inherited complex neural circuits which drive behavioural, somatic, and autonomic thermoregulatory responses to defend their body temperature. While they are well adapted to dissipate heat in warm climates, they have a reduced capacity to preserve it in cold environments.¹ Shivering, which usually occurs as a thermoregulatory response to cold, and the body's next step in heat preservation after peripheral vasoconstriction.² Although shivering may have beneficial thermoregulatory effects, it places the body under increased physiological stress.³ Shivering, a syndrome involving involuntary oscillatory contractions of skeletal muscles is a common and challenging side effect of anaesthesia and targeted temperature modulation.⁴ Shivering is believed to increase oxygen consumption, increase the risk of hypoxemia, induce lactic acidosis, and catecholamine

release and is usually triggered by hypothermia.

Both general and regional anaesthesia is known to affect the efficiency of this homeostatic system and may result in different degrees of perioperative hypothermia. Regional anaesthesia also decreases this threshold by 0.5°C, triggering vasoconstriction and shivering above the level of block. this reduction in threshold is proportional to the number of spinal segments blocked, advanced age and high-level spinal blockade.^{5,6} Post-anaesthesia shivering is a common complication following subarachnoid block (SAB); reported incidence varying from 40% to 70%.⁷

Subarachnoid block with local anaesthetics and opioids enable efficacious spinal anaesthesia because of their synergistic effect and permit the use of low-dose local anaesthetics, which results in a stable hemodynamic state.^{8,9} In addition to the fact that shivering is poorly understood, the gold standard for the treatment and prevention has not been defined yet.¹⁰

Postoperative shivering in patients severely increases oxygen consumption (400 times) which is followed by a rise in CO₂ production leading to acidosis when the alveolar ventilation is not increased proportionally.¹¹ Ketamine, derived from phencyclidine, is an agent used in dissociative anaesthesia and characterised by thalamus and limbic system separation on the electroencephalograph (EEG). Fast-acting and fat solubility of ketamine guarantee its rapid onset.¹² Ketamine is an anaesthetic agent and non-competitive antagonist of N-methyl D-aspartate (NMDA) which in lower subanaesthetic doses has analgesic effects, regulates temperature in multiple stages and prevents shivering.^{13,14}

The aim of the current study was to compare the efficacy of two different doses of ketamine 0.25mg.kg⁻¹, 0.5mg.kg⁻¹ with placebo (normal saline) to prevent shivering during the subarachnoid block inpatient undergoing elective surgery.

¹Medical Officer, Department of Anesthesiology and Critical Care, Civil Hospital, Aizawl, Mizoram, ²Consultant, Department of Anaesthesiology, Civil Hospital, Aizawl, Mizoram.

Corresponding author: Dr. Lalnunmawii Sailo, Civil Hospital, Aizawl, Mizoram

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MATERIAL AND METHODS

The present study was a prospective randomized double-blind placebo-controlled trial, conducted in the various operating rooms and postoperative recovery rooms in Institute Civil Hospital, Aizawl, Mizoram from March 2017 to August 2018.

ASA I and II patients of either sex between the ages of 18 – 60 years undergoing elective infra-umbilical surgery under subarachnoid blocks were included in the study. Those who failed to fulfil this criterion were subjected to exclusion from the study.

Total of 90 participants sample size was achieved by previous studies which had found an incidence of shivering of the order of 40 – 65%. With the anticipation of incidence of 45% in the control group and a difference of 40% in the incidence of shivering between control and treated groups as being clinically meaningful, 30 patients were required in each group for a type I error of 0.05 and a type II error of 0.2. The patients were randomly allocated into 3 groups using computer-generated random number sequence viz. Group1: ketamine at dose of 0.5 mg /kg (n=30), Group2: ketamine at dose of 0.25 mg /kg (n=30), Group3: saline (n=30). Allocation concealment was done using serially numbered opaque sealed envelopes. The treatment drugs were diluted to a volume of 4 ml and presented as coded syringes by an anesthesiologist who was blinded to the group allocation.

Study procedure

Complete pre and aesthetic evaluation was performed in each patient including detailed history taking, thorough physical check-up, assessment of spine, airway examination and assessment of routine investigations, like complete hemogram, fasting blood sugar (FBS) and postprandial blood sugar (PPBS), urea, creatinine, ECG 12 leads & Chest X-ray (PA View)

Under strict aseptic precaution, the subarachnoid block was instituted at either L3/4 or L4/5 interspaces with hyperbaric bupivacaine 0.5%, using a 25 G Quincke's spinal needle. Just after intrathecal injection, study drug was injected as an IV bolus according to group allocation.

Parameters studied

Heart rate, mean arterial pressure, respiratory rate and peripheral oxygen saturation were monitored and recorded using standard non-invasive multichannel monitors before and after intrathecal injection and at 10 min intervals during

the perioperative period.

Body temperature (nasopharyngeal and axillary temperature) were recorded with a nasopharyngeal and an axillary thermometer at 10 minutes interval. The ambient temperature was measured by a wall thermometer and was maintained at 24.8°C.

Shivering will be graded using a scale similar to that validated by Tsai and Chu. Side-effects, such as hypotension, sedation, nausea and vomiting, and hallucinations were recorded.

Ethical considerations

At the pre-anaesthesia visit, patients were explained regarding the study protocol and written informed consent was obtained from all the patients prior to including them in the study.

STATISTICAL ANALYSIS

Study group was considered as explanatory variables. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Non-normally distributed quantitative variables were summarised by median and interquartile range (IQR).

All Quantitative variables were checked for normal distribution within each category of an explanatory variable by using visual inspection of histograms and normality Q-Q plots. Shapiro-wilk test was also conducted to assess normal distribution. Shapiro-wilk test p value of >0.05 was considered as normal distribution.

For normally distributed Quantitative parameters, the mean values were compared between study groups using Independent sample t-test (2 groups). For non-normally distributed Quantitative parameters, Medians and Interquartile range (IQR) were compared between study groups using Mann Whitney u test (2 groups)

Categorical outcomes were compared between study groups using the Chi square test

P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.¹⁵

RESULT

In this study, 90 adult patients (ASA physical status I and II) were randomly allocated to receive either ketamine 0.50mg/kg or ketamine 0.25mg/kg or normal saline infusion. All the three study groups were comparable with respect to all the baseline variables, including age, gender, weight, height

Parameter	Group			P Value
	1 (Ketamine 0.5 mg /kg)	2 (Ketamine 0.25 mg /kg)	3 (Normal saline)	
Age (in years)	42.6 ± 11.174	39.87 ± 10.52	38.00 ± 11.84	0.283
Weight	59.63 ± 9.597	59.90 ± 9.568	61.13 ± 10.776	0.85
Height	160.63 ± 7.845	161.83 ± 10.469	154.50 ± 7.533	0.103
Duration of surgery	76.67 ± 5.467	76.67 ± 5.467	79.00 ± 3.051	0.100
Gender				
Female	13(30.95%)	14(33.33%)	15(35.71%)	0.875
Male	17(35.41%)	16(33.33%)	15(31.25%)	

Table-1: Comparison of age (in years) between the three groups

Parameter	Nasopharyngeal Temperature (TN)			P Value
	1	2	3	
TNB	36.1±0.444	35.76±0.266	35.68± 0.142	P=0.000
TNA	36.08± 0.436	35.74± 0.268	35.68±0.145	P=0.000
TNS	36.01±0.438	35.67± 0.278	35.58±0.142	P=0.000
TNK	35.98±0.443	35.63± 0.264	35.55± 0.048	P=0.000
TN10	35.87±0.42	35.56± 0.276	35.47±0.050	P=0.000
TN20	35.78±0.399	35.52± 0.261	35.43± 0.151	P=0.000
TN30	35.69±0.389	35.45± 0.278	35.36± 0.133	P=0.000
TN40	35.61±0.388	35.41± 0.258	35.32±0.152	P=0.001
TN50	35.55±0.384	35.31± 0.311	35.24± 0.143	P= 0.000
TN60	35.47±0.38	35.27±0.307	35.19±0.142	P=0.001
TN70	35.4±0.386	35.14± 0.459	35.13± 0.149	P=0.007
TN80	35.36±0.39	35.12± 0.455	35.07± 0.166	P=0.006
TNE	35.24±0.422	35.05± 0.413	34.95± 0.161	P=0.007
TNP10	35.19±0.436	35± 0.423	34.9± 0.167	P=0.009
TNP20	35.08±0.527	34.95± 0.413	34.84±0.159	P=0.070
TNP30	35.04±0.525	34.9± 0.426	34.78± 0.163	P=0.044
Parameter	Axillary Temperature (TA)			P Value
	1	2	3	
TAB	34.15 ± 0.825	35.16 ± 0.393	35.31 ± 0.108	P=0.000
TAA	34.12 ± 0.831	35.12 ± 0.391	35.3 ± 0.105	P=0.000
TAS	34.04 ± 0.796	35.06 ± 0.394	35.21 ± 0.105	P=0.000
TAK	33.9 ± 0.768	34.99 ± 0.404	35.18 ± 0.119	P=0.000
TA10	33.91 ± 0.559	34.93 ± 0.409	35.1 ± 0.110	P=0.000
TA20	33.92 ± 0.814	34.88 ± 0.401	35.06 ± 0.110	P=0.000
TA30	33.82 ± 0.832	34.82 ± 0.416	34.99 ± 0.114	P=0.000
TA40	33.69 ± 0.759	34.78 ± 0.397	34.94 ± 0.110	P=0.000
TA50	33.63 ± 0.753	34.7 ± 0.404	34.87 ± 0.118	P=0.000
TA60	33.54 ± 0.751	34.67 ± 0.398	34.82 ± 0.134	P=0.000
TA70	33.48 ± 0.739	34.6 ± 0.403	34.75 ± 0.122	P=0.000
TA80	33.46 ± 0.725	34.57 ± 0.384	34.7 ± 0.136	P=0.000
TAE	33.39 ± 0.722	34.46 ± 0.370	34.59 ± 0.117	P=0.000
TAP10	33.32 ± 0.689	34.43 ± 0.360	34.53 ± 0.131	P=0.000
TAP20	33.27 ± 0.705	34.37 ± 0.372	34.52 ± 0.210	P=0.000
TAP30	33.43 ± 1.391	34.33 ± 0.370	34.47 ± 0.240	P=0.003
Parameter	Shivering Scale SS (Tsai & Chu)			P Value
	1	2	3	
SSB	ND	ND	ND	ND
SSA	ND	ND	ND	ND
SSS	ND	0.07±0.254	0.1±0.305	P=0.000
SSK	ND	0.1±0.305	0.4±0.498	P=0.000
SS10	0.10±0.305	0.1±0.305	0.53±0.681	P=0.000
SS20	0.13±0.346	0.1±0.305	0.73±0.828	P=0.000
SS30	0.07±0.254	0.1±0.305	0.93±1.081	P=0.000
SS40	0.03±0.183	0.07±0.254	0.93±1.112	P=0.000
SS50	0±0	0.03±0.183	0.83±0.23	P=0.000
SS60	ND	ND	0.7±1.291	ND
SS70	ND	ND	0.5±0.1.042	ND
SS80	ND	ND	0.4±1.070	ND
SSE	ND	ND	0.27±0.740	ND
SSP10	ND	ND	0.23±0.679	ND
SSP20	ND	ND	0.13±0.434	ND
SSP30	ND	ND	0.13±0.571	ND

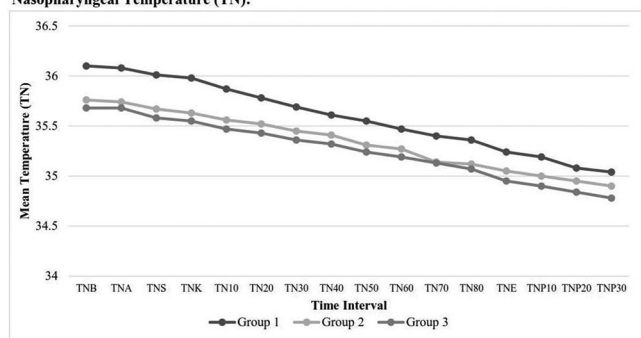
(B- baseline, A-after spinal block, S- the start of surgery, K- ketamine injection, at 10 mins interval, E- end of surgery, Post-operative (P) 10 mins interval till 30 minutes)

Table-2: Nasopharyngeal Temperature (TN) variation between three groups

Parameter	Group		
	1	2	3
Sedation			
1	19 (27.14%)	21 (30%)	30 (42.86%)
2	8 (47.06%)	9 (52.94%)	0 (0%)
3	3 (100%)	0 (0%)	0 (0%)
Hallucinations			
Negative	27 (30.0%)	30 (33.3%)	30 (33.3%)
Positive	3 (3.3%)	0 (0.0%)	0 (0.0%)
Hypotension			
Negative	23 (25.6%)	28 (31.1%)	27 (30.0%)
Positive	7 (7.8%)	2 (2.2%)	3 (3.3%)
Nausea & Vomiting			
Negative	26 (28.9%)	27 (30.0%)	27 (30.0%)
Positive	4 (4.4%)	3 (3.3%)	3 (3.3%)

Table-3: Comparison of sedation between the three groups using the chi square test

Nasopharyngeal Temperature (TN):



Axillary Temperature (TA):

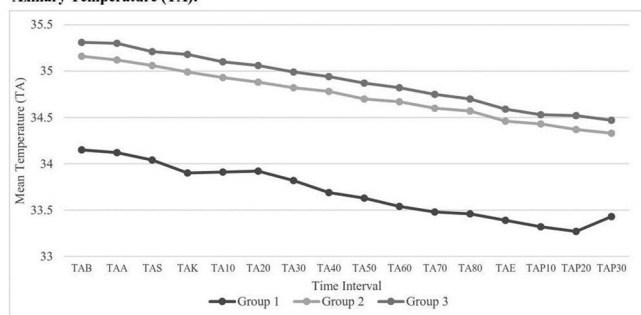


Figure-1:

and duration of surgery, with no statistically significant differences (P value > 0.05) (Table 1)

Compared with baseline mean core temperature the mean difference between the lowest temperature, i.e. postoperative at 30 mins in group 1 is 1.06°C, in group 2 it is 0.86°C, and in group 3 it is 0.90°C. The decreases in core temperatures were statistically significant in Groups 1, 2, and 3 when compared with the baseline level (P<0.05). (Table 2)

Compared with baseline mean axillary temperature the mean difference between the lowest temperature, i.e. postoperative at 30 mins in group 1 is 0.88°C, in group 2 it is 0.83°C, and in group 3 it is 0.84°C. The decreases in axillary temperatures were statistically significant in Groups 1, 2, and 3 when compared with the baseline level (P<0.05). (Table 2)

After spinal anaesthesia and concomitant administration of the study drug, shivering was observed only in 10% of patient with score 1 in Group 1 and Group 2. Whereas in

placebo group 50% patients suffered different degrees of shivering and required treatment (p<0.05).

After 10 min of spinal analgesia, Grade 4 shivering was observed in 13.3% of patient in Group 3 and none in Group 1 and 2. Grade 3 shivering was observed in 3.3% of patient in Group 3 and none in group 1 and 2. These patients were subsequently treated with i.v. Tramadol 50 mg.). (Table 2) Group 1 had significantly higher heart rate and respiratory rate, whereas the mean arterial blood pressure was significantly lower in group 1(p<0.05). Oxygen Saturation (SPO2) between the three groups 1, 2 and 3 were comparable group at all times (p<0.05). (Figure 1)

The sedation score was 1 in all patients just after intrathecal injection and before giving treatment drugs. However, after study drug injection % of a patient having sedation score 3 was significantly higher in Group 1 (3%) than Groups 2 and 3 (0%) (P=0.002). % of patient having sedation score 2 was significantly higher in Group 1 (8.9%) and group 2 (10%) than in Group 3 (P=0.002). Only 3.3% patients of group1 experienced hallucination and rest of the patients in any group had no hallucination (P value= 0.045) No of patient having nausea and vomiting were comparable in all three groups with P value= 0.133. No of patient experiencing nausea and vomiting were comparable in all three groups with P value= 0.894. (Table 3)

DISCUSSION

Shivering and vasoconstriction originate from the hypothalamus in response to hypothermia related to neuraxial anaesthesia. Hypothermia occurring in neuraxial anaesthesia is due to vasodilatation and internal redistribution of heat.¹⁶ Shivering is elicited when the preoptic region of the hypothalamus is cooled.¹⁷ Postoperative shivering is a common problem emerging from the general anaesthesia in the recovery room that occurs in 5 to 65 per cent of patients. This condition is very inconvenient for patients. Postoperative shivering is a phenomenon regulated by temperature (a physiological response to anaesthesia-induced central hypothermia) or triggered by cytokine release induced by surgical procedures.¹⁸

The results of this prospective, randomised, double-blind, placebo-controlled study revealed that ketamine at dose of 0.5 mg /kg had similar effects as that of ketamine at dose of 0.25 mg /kg when compared to saline group. We observed that almost half of the participants of group 3 After spinal anaesthesia and concomitant administration of the study drug presented with different degrees of shivering. Grade 3 and 4 shiverings was observed only in among participants of group 3. Dal et al¹⁹, in their study found that the number of patients shivering on arrival in the recovery room, and at 10 and 20 min after operation were significantly less in Groups P (pethidine 20 mg) and K (ketamine 0.5 mg kg (-1)) than in Group S (normal saline). The time to first analgesic requirement in Group S was shorter than in either Group K or Group P (P<0.005). Hence concluded that use of Prophylactic low-dose ketamine was very useful in preventing postoperative shivering. Genopadhyay et al²⁰ concluded that pethidine, tramadol and ketamine effectively prevent shivering following spinal anaesthesia, prove ketamine was smart and effective alternative over two drugs due to the better haemodynamic stability and less adverse effect. A randomised, double-blind clinical trial conducted previously resulted that ketamine, doxapram and meperidine are equally effective in the prevention of postoperative shivering.²¹

No major hemodynamic changes were seen with prophylactic use of test drugs, and there was a greater fall in core body temperatures in the placebo group as compared with the ketamine. Our results matched with the study conducted by Wason et al²², and Sagir et al.²³

We found that sedation score 3 was higher among participants of group 1 compared to participants in group 2 and 3. Also, our finding state that hallucination was experienced by few study subjects of group 1 whereas none both the other groups had hallucinations. Study results also said that No of patient having nausea and vomiting and hypotension were comparable in all three groups. The incidence of hallucination, nausea, vomiting, bradycardia, and tachycardia was not statistically significant.²⁴ Bell et al²⁵, in their study found that Ketamine-treated patients showed less postoperative nausea and vomiting. The frequency of nausea and hypotension (systolic pressure, <90 mmHg) was significantly higher in group S (epidural administration of normal saline; n=30) compared with group K, (epidural ketamine 0.5 mg/kg; n=30).²⁶

Our study saw that ketamine at a dose of 0.5 mg /kg and ketamine at dose of 0.25 mg /kg have a significant effect in prevention of shivering in the patients undergoing elective infra-umbilical surgery under subarachnoid blocks. Lema, GF et al²⁷, determined in their study that incidence of shivering was significantly reduced in the ketamine group (41.5%) compared to the saline group (70.7%; p=0.028) and prophylactic administration of low-dose IV ketamine is effective for reducing the incidence and intensity of shivering and can be recommended for patients undergoing cesarean section under spinal anaesthesia. Similarly, the study by Hasannasab, B et al²¹, and Xue, X et al²⁶, also showed that ketamine is effective in the prevention of postoperative

shivering.

In summary, the results of the present study suggest that prophylactic epidural administration of low-dose ketamine is able to reduce the incidence and severity of shivering in patients undergoing elective infra- umbilical surgery under subarachnoid blocks. However, the present study focused on the occurrence and prevention of intraoperative shivering and only investigated single-dose ketamine. Future studies should investigate the potential of ketamine to reduce postoperative shivering in the future and seek to elucidate the optimal dose.

CONCLUSION

The present research concludes that the shivering effect was poorly present among participants of group 1 and 2. Which concludes ketamine at dose of 0.5 mg /kg had similar effects as that of ketamine at dose of 0.25 mg /kg when compared to placebo group. In this study we observed that ketamine at dose of 0.5 mg /kg caused higher effects of seduction and hallucination than ketamine at dose of 0.25 mg /kg group.

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