



## EFFECT OF PREEMPTIVE CLONIDINE VERSUS PETHIDINE AND KETAMINE ON POSTOPERATIVE SHIVERING DURING SPINAL ANESTHESIA

### Anaesthesiology

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### ABSTRACT

**Background:** Postoperative Shivering is an early postoperative complication. Incidence of postoperative shivering (POS) following surgeries varies between 20 to 60%. There is still no consensus on treatment modalities especially in opioid-dependent patients. **Aim:** To compare the effect of preemptive clonidine, ketamin and pethidine in controlling postoperative shivering in addicted patients who undergo spinal anesthesia. **Methods:** In a clinical trial, 81 patients who underwent spinal anesthesia for elective orthopaedic surgery for lower limb were enrolled and assigned to groups of 27 patients of the study based on accidental numbers, and 2 patients in Pethidine group and 2 patients in ketamine group were excluded from the study. Clonidine 2 mg was administered orally prior to surgery. Ketamin 2mg/kg and pethidine 0.5 mg/kg were administered in recovery to the patients. Postoperative shivering was measured in patients during stay in post anesthesia care unit. Blood pressure and heart rate was recorded during 30 minutes after spinal anesthesia in operating room. **Results:** No significant differences in blood pressure and heart rate were observed between patients. Incidence of postoperative shivering was 28% in clonidine, 36% in pethidine and 48% in ketamine group. Risk of shivering was significantly reduced in patients received clonidine in compare to ketamine (RR: 0.34, 95% CI: 0.138-0.856, p=0.022) which was significant and compare to pethidine (RR=0.79, 95% CI: 0.272-2.323, p=0.67) which was not significant. **Conclusion:** preemptive Clonidine has superior effect compare to postoperative ketamin and pethidine in controlling postoperative shivering.

### KEYWORDS

Clonidine, Ketamine, Pethidine, Postoperative, Shivering, Spinal Anesthesia

### INTRODUCTION

Postoperative shivering (POS) is an early postoperative complication following spinal anesthesia. Postoperative shivering incidence has been reported between 20 to 60% (Manninen, Raman, Boyle, & el-Beheiry, 1999). Hypothermia is a common finding during anesthesia. General anesthesia could significantly impact thermoregulatory process. Ppostoperative shivering in general anesthesia is mainly induced by hypothermia while thermoregulation is deeply suppressed by anesthetics (Zhang & Wong, 1999). Shivering enhances metabolic heat production upto 50% to 100% in adults. However, this increase is not effective during general anethseia compare to severe heat loss (Eberhart et al., 2005).

Preventive pharmacologic therapies are alternative treatment for post-operative shivering (Mahmood & Zweifler, 2007). Non-pharmacologic approaches such as maintaining room temperature, warmers and air blankets (H. Y. Kim et al., 2014) and hot intravenous infusions have variable effect (Alfonsi, 2003). Duration of anesthesia is a risk factor for POS (Crossley, 1992). POS could increase myocardial oxygen consumption and cardiovascular events.

Although the wax-and-wane pattern of post shivering is a thermoregulatory response to intraoperative hypothermia; however; neurotransmitter pathways playing role in POS are poorly understood. POS may result from dis-inhibition of normal cortical control of spinal reflexes induced anesthesia.

Many drugs are introduced as treatment for POS including pethidine, clonidine, and physostigmine. Opioids, alpha 2-adrenergics (Hwang, 2014), Ketamine (Dal et al., 2005), and anticholinergics are other choices. Other drugs such as Tramadole (Heid et al., 2008), Nefopam (Rosa et al., 1995), Ketanserin a 5-HT<sub>2</sub> antagonist has also been used for prevention of POS (Y. A. Kim et al., 2013). Although Tramadole and Pethidine are available drugs for prevention of POS, however, both drugs could increase intra cranial pressure (ICP) and increase risk of seizure. Clonidine is an  $\alpha_2$ -agonist with both central and peripheral effect (Eisenach, De Kock, & Klimscha, 1996). It passes the blood brain barrier and reaches the hypothalamus and medulla. It decreases the excitatory sympathetic neuron impulses.

### OBJECTIVES

To compare the Effect of Clonidine, ketamine and Pethidine on postoperative shivering during Spinal Anesthesia.

### MATERIALANDMETHODS

#### Patient Selection

Present study was conducted at Department of Anaesthesia associated with Department of Orthopaedics, Sri Krishna Medical and Hospital, Muzaffarpur, Bihar.

Total of 81 patients with ASA class I to II, age between 20 to 60 years, BMI less than 30 kg/m<sup>2</sup>, no history of hyper or hypothyroidism or Parkinson's disease, and scheduled for elective lower extremity surgery were included in the study. Patients were divided to receive clonidine, ketamine, and pethidine. Patients were excluded if they had perioperative fever (temperature>38), received blood transfusion more than 4 units of pack cells, or used medications to alter thermoregulation during surgery.

#### Study Design

This study was designed as a double blinded randomized clinical trial. Randomization was performed based on accidental numbers assigned to each patient by computer. Anesthesiologists performing evaluation were blinded to the group of patient. Patients were also blinded to the drug that was administered. Drugs were also delivered in the same size syringe and same color to the anesthesiologist performing spinal anesthesia (concealment allocation). Duration of study was 1 year period from February 2019 to January 2020.

Eighty one patients were enrolled in the study and assigned to groups of 27 patients; group Clonidine, Ketamine, and Pethidine. Two patients in Pethidine group and 2 patients in ketamine group were excluded from the study. Anesthesiologist administering drug was not aware of group of patient and syringe content (allocation concealment). Besides, physician who evaluated the shivering and other monitoring were not aware of group of patient.

Clonidine 0.2 mg oral was administered 1 hour before surgery. Ketamine 2 mg/kg and Pethidine 0.5 mg/kg was administered after

surgery in recovery room.

**Method of Anesthesia**

Spinal anesthesia was performed by patient in sit position, and L3-4 space, needle G25, and Bupivacaine isobaric 0.5% 4 ml equal to 20 mg was injected into sub-arachnoid space. Patients were covered with 3 layers of surgical drapes. The ambient temperature was measured and set by a wall thermometer to room temperature at 23.0 C.

**Data Collection**

Demographic variables were recorded in specified data sheet for all patients. Heart rate and blood pressure were recorded during surgery. Presence of shivering in recovery was also recorded as positive or negative.

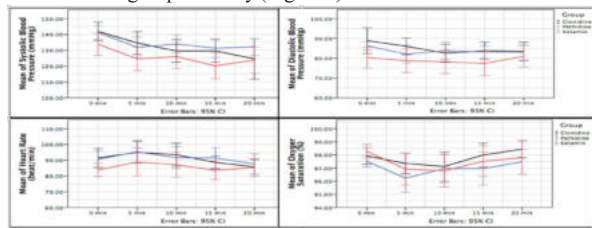
**RESULTS**

In this study, total numbers of 81 patients were enrolled and 2 patients in Pethidine group and 2 patients in ketamine group were excluded from the study. The age was significantly higher in pethidine group but was not significantly different between ketamine and clonidine group. Axillary temperature was measured between 36.5-37.5 C degrees in all patients (100% of patients) in three groups of study (Table 1).

**Table 1 : Comparison Of Age, Opioid Abused And Patients With Normal Axillary Temperature**

	Clonidine N=25	Pethidine N=25	Ketamin N=27	P-value
Age	34.52±10.15	44.48±12.22	39.85±15.48	0.028
Type of opioid	0 (0%)	4 (16.7%)	8 (34.8%)	
Synthetic				
Semi-synthetic	5 (20.0%)	4 (16.7%)	2 (8.7%)	
Naturally	19 (76.0%)	10 (41.7%)	10 (43.5%)	0.005
Amphetamine	1 (4.0%)	6 (25.0%)	3 (13.0%)	
Unknown	0	1	4	
Axillary temperature 36.5-37.50	25 (100%)	25 (100%)	27 (100%)	NA

Systolic blood pressure and diastolic blood pressure were not significantly different at various time points between three groups of study (p>0.05) in ANOVA analysis. Heart rate was not significantly different at various time points between three groups of study. Oxygen saturation was not also significantly different at various time points between three groups of study (Figure 1).



**Figure 1. Trend of systolic and diastolic blood pressure, heart rate, and oxygen saturation in post-operative time points**

Percentage of patients with post-operative shivering was lower in clonidine group compare to ketamine and pethidine groups but it was not significant (Table2).

**Table 2 : Post-operative Shivering In Three Groups Of Study**

Shivering	Clonidine	Pethidine	Ketamin	P-value
0 min	1 (4.0%)	1 (4.0%)	2 (7.4%)	>0.999
5 min	6 (24.0%)	9 (36.0%)	11 (40.7%)	0.425
10 min	6 (24.0%)	8 (32.0%)	10 (37.0%)	0.594
15 min	3 (12.0%)	6 (24.0%)	7 (25.9%)	0.414
20 min	0 (0.0%)	3 (12.0%)	4 (16.0%)	0.150
Post-operative	7 (28.0%)	9 (36.0%)	13 (48.1%)	0.319

In a GEE (Generalized Estimating Equations) model analysis the relative risk (RR) of shivering was 0.36 times in clonidine compare to ketamine and was 0.63 times in clonidine compare to pethidine group. When adjusted for age, RR of shivering was 0.34 times in clonidine compare to ketamine and was 0.79 times in clonidine compare to pethidine group (Table3).

**Table 3 : Generalized Estimating Equations (GEE) Analysis The Relative Risk (RR) Of Shivering**

GEE for Shivering	P-value	RR
<b>Non-adjusted</b>		
Clonidine/Ketamin	0.033	0.369 (0.148-0.921)
Pethidine/Ketamin	0.621	0.781 (0.293-2.079)
Clonidine/Pethidine	0.394	0.637 (0.226-1.795)
<b>Adjusted for Age</b>		
Clonidine/Ketamin	0.022	0.344 (0.138-0.856)
Pethidine/Ketamin	0.620	0.765 (0.264-2.210)
Clonidine/Pethidine	0.675	0.795 (0.272-2.323)
<b>Adjusted for Age &amp; Drug groups</b>		
Clonidine/Ketamin	0.130	0.448 (0.159-1.262)
Pethidine/Ketamin	0.112	0.406 (0.134-1.234)
Clonidine/Pethidine	0.883	1.103 (0.298-4.092)

**DISCUSSION**

Here in this study, we embarked on a shivering in peri and post-operative period in opioid-dependent patients. Shivering is one of the most common problems during and after spinal anesthesia. Treatment of shivering in opioid-dependent patients after spinal anesthesia is still controversial and needs further researches. Results of our study showed that clonidine has superior effect to ketamine and pethidine in controlling shivering in opioid-dependent patients.

Clonidine is alpha-2-agonists that inhibit central sympathetic stimulation. Clonidine is orally administered and easy to use for preventive effect in shivering. Dexmedetomidine has been proved to have central effect on controlling shivering in patients (Liu et al., 2015). However, its effect in opioid-dependent patients has not been published previously. Unlike oral clonidine, Dexmedetomidine could induce profound hypotension and bradycardia when used intravenously.

Pre-operative clonidine is an appropriate choice in controlling post-operative shivering in opioid-dependent patients which start its preventive action prior to starting neuroaxial anesthesia. Mechanism of action for clonidine is through central decrease in threshold of temperature for shivering and vasoconstriction. In a systematic review by Kranke et al; they showed that clonidine, pethidine and ketanserin are appropriate pharmacological treatment of postoperative shivering (Kranke, Eberhart, Roewer, & Tramer, 2002).

Pethidine has proven pharmacological effect on postoperative shivering through k-receptor; however, opioid-dependent patients could have tolerance of opioid receptors including k receptor. This may explain lower effectiveness of pethidine in opioid-dependent patients compare to normal population. Ketamine has also effect on modulation of NMDA receptor function to decrease tolerance to opioids in opioid-dependent patients (Hollmann, Liu, Hoenemann, Liu, & Durieux, 2001). However, ketamine effect on postoperative shivering is not far more than clonidine or Pethidine in opioid-dependent patients. Vice versa, Suzuki et el showed that perioperative ketamine increased the incidence of POS induced by remifentanyl (Suzuki, Osumi, Shimada, & Bito, 2013). Remifentanyl-induced shivering is a model for opioid-dependent patients. This was consistent with our results that ketamine is not more effective in controlling shivering than pethidine in opioid-dependent patients.

Other studies such as Tewari et al (Tewari et al., 2014), evaluating the prophylactic efficacy of oral clonidine and tramadol for peri-operative shivering in geriatric patients undergoing transurethral resection of prostate; they showed that 5% in clonidine and 7% in tramadol group had shivering which there were no significant differences between two groups of study. In another similar study by Wason et al, prophylactic ketamine had no superior effect to clonidine and tramadol in controlling and decreasing POS (Wason, Jain, Gupta, & Gogia, 2012). Interestingly, unlike clonidine in our study, Bhukal et al showed that low dose pethidine does not decrease incidence of postoperative shivering in laparoscopic surgeries (Bhukal, Solanki, Kumar, & Jain, 2011). Recent publications have mentioned effect of preemptive Dopamine antagonist such as ondancetrone and granicetrone in decreasing post-operative shivering (Sagir et al., 2007; Teymourian et al., 2015).

**CONCLUSION**

In conclusion, pre-operative oral clonidine has a superior effect in

controlling postoperative shivering compare to postoperative intravenous pethidine and ketamine in opioid-dependent patients.

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