

Comparison of Pethidine and Ketamine for the Treatment of Postoperative Shivering

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ABSTRACT

Objective: To compare the effectiveness of Ketamine vs Pethidine for treating postoperative shivering in patients undergoing surgery under general anaesthesia.

Study Design: Quasi-experimental study.

Place and Duration of Study: Operation Theatre, Combined Military Hospital Sialkot Pakistan, from Jan to Apr 2020.

Methodology: Following strict inclusion and exclusion criteria, patients who experienced postoperative shivering in the post-anaesthesia care unit (recovery) were enrolled through consecutive sampling and randomized into group-A or group B using the lottery method. Group-A received Pethidine 0.5 mg/kg and Group-B received Ketamine 0.2 mg/kg. The shivering grade was evaluated at 0 minutes and 5 minutes after administration of drugs by using a validated four-point scale.

Results: Mean age of the patients was 34.12 ± 9.88 years and 34.83 ± 9.77 years in group-A and group B, respectively. At 5 min, the recovery rate of shivering was significantly higher in the Pethidine group than in the Ketamine group. In group-A, effectiveness (grade 0) was noticed in 124 patients (86.2%) and in group-B effectiveness (grade-0) was seen in 74 patients (51.4%). A statistically significant difference ($p < 0.01$) was found between the two groups.

Conclusion: Pethidine 0.5 mg/kg is a more effective drug for treating postoperative shivering.

Keywords: Ketamine, Pethidine, Postoperative Shivering.

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INTRODUCTION

Postoperative shivering is one of the most prevailing problems in the recovery period after general and regional anaesthesia. According to various studies, the incidence of shivering is 5-65% in patients emerging from general anaesthesia and up to 57% in patients recovering from neuraxial anaesthesia.¹ Shivering is defined as detected fasciculation or tremor of the jaw, head, face, trunk or extremities lasting longer than 15 sec.²

Shivering is associated with an upsurge in cardiac and systemic energy expenditure, increases metabolic rate up to 400%,³ increases oxygen consumption 200-500%,⁴ decreases tissue oxygenation, and increases carbon dioxide production up to three times. It increases heart rate, cardiac output, left ventricular systolic work index and peripheral vascular resistance. In addition, it increases the release of catecholamines, causes lactic acidosis and raises intracranial and intraocular pressures.⁵ Hypothermia and shivering are coupled with increased myocardial ischemia, arrhythmias, coagulopathy with increased requirements for transfusion of blood products, and delayed emergence from

anaesthesia.⁶ It also interferes with hemodynamic monitoring intraoperatively, including interference in monitoring oxygen saturation (SPO₂), Electrocardiogram (ECG), and fluctuations in the blood pressure recording.⁷ Shivering may be more dangerous for patients with low cardio-respiratory reserves.³

According to a meta-analysis of randomized controlled trials, the five most frequently studied and efficacious anti-shivering drugs are Clonidine, Pethidine, Tramadol, Ketamine and Nefopam.⁸ Pethidine, a synthetic opioid, inhibits shivering by acting on the κ receptor, which reduces vascular constriction threshold and has an anticholinergic activity.⁹ Ketamine, a phencyclidine derivative, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, inhibits shivering by acting on the hypothalamus. The betaadrenergic affects norepinephrine and decreases core to peripheral redistribution of heat.¹⁰

The rationale of this study was to find out a more effective anti-shivering agent by comparing the effectiveness of Ketamine vs Pethidine in two groups of patients (group-A and group B) in the post-anaesthesia care unit (PACU). Based on statistics, treating shivering can enable us to sidestep its adverse effects on different systems of the patient's body, particularly the cardiovascular system. Therefore, the primary out

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come was to compare the decrease in the number of cases of postoperative shivering after injecting the drug intravenously.

METHODOLOGY

It was a quasi-experimental study conducted at the Operation Theatre of Combined Military Hospital, Sialkot Pakistan, from Jan to Apr 2020. Ethical approval was obtained (ERC/05/2020) from the Hospital Ethical Committee. The sample size was calculated using the WHO sample size calculator, keeping power of 90% and a significance level of 5%. According to Eydi *et al*,⁵ minutes after administration of Pethidine, 9 out of 30 patients did not recover. Still, they had shivering grades 1-4, while in the Ketamine group, 14 out of 30 were having shivering. The effectiveness of Pethidine for the treatment of postoperative shivering was 70%, while Ketamine was 53.33%.¹¹ The sample size was 144 in each group. The total sample size was 288. The sampling technique was consecutive sampling with random allocation.

Inclusion Criteria: Patients of either gender, aged between 18-55 years, having ASA status I & II, undergoing planned surgery with the duration of surgery, not more than 2 hours were included in the study.

Exclusion Criteria: Patients having a known history of hypersensitivity to any of the study drugs, history of hypothyroidism or hyperthyroidism, 20% more than the ideal body weight or taking anti-depressants/anti-psychotics were excluded from the study.

Patients were interviewed, explained and counselled about the purpose of the study, procedure and risk-benefit ratio of administering Pethidine and Ketamine intravenously and informed written consent was obtained in the pre-anaesthesia clinic.

The operating room and PACU (Recovery Room) temperatures were maintained at 24°C. All fluids were kept at room temperature for 24 hours before use. Injection dexamethasone 4mg and Injection metoclopramide 10mg were administered intravenously upon the patient's arrival in the operation room. Patients were given Propofol 2.5 mg/kg, Nalbuphine 0.1mg/kg and Atracurium 0.5mg/kg intravenously. Anaesthesia was maintained with 1.5-2% Isoflurane. Neuromuscular blockade was reversed with Injection of Neostigmine 2.5mg ± Injection of Glycopyrrolate 0.5mg. All patients in PACU received blanket and O² @ 5L/min by facemask.

Patients eligible for the study who experienced shivering in PACU were randomly divided into

groups A or B using the lottery method. Patients were blinded to treatment allocation. Group-A received Pethidine 0.5 mg/kg and Group-B received Ketamine 0.2 mg/kg. The shivering grade was evaluated at the time of drug administration, "0" minute and again after 5 minutes of drug administration, using the following scale first described by Lopez *et al*,² 0-no shivering, 1-mild fasciculation of the face or neck/ecg disturbances, 2-visible tremors that involved more than one muscle group, 3-gross muscular activity that affected the entire body.

Statistical Package for Social Sciences (SPSS) version 21.0 was used for the data analysis. Mean ± SD were calculated for numerical values like age, weight, and height. Frequency and percentages were calculated for categorical variables like gender and shivering. The Chi-square test was used for the comparison of qualitative findings. The *p*-value ≤0.05 was taken as significant. All results were presented in the form of tables and graphs.

RESULTS

Out of 288 respondents (144 included in each group), 183 (64%) were male, and 105 (36%) were female. In group-A, 97 patients (67.4%) and in group B, 86 patients (59.7%) were male, while 47 patients (32.6%) of group-A and 58 patients (40.3%) of group B were female. Patients' age ranged from 18-55 years of age. The mean age, weight and height of group-A and group B, along with standard deviations, were shown in the Table-I.

Table-I: Distribution of patients by age, weight and height.

Groups	Age (Years)	Weight (Kg)	Height (Ft)
A (Mean ± SD)	34.12 ± 9.88	69.50 ± 9.94	5.65 ± 0.35
B (Mean ± SD)	34.83 ± 9.77	67.63 ± 11.28	5.65 ± 0.36

Shivering grades were evaluated at 0 minutes. The distribution of patients in both groups according to their grades of shivering (I-III) were shown in the Table-II. Statistically, no significant difference was seen in both groups at 0 min (*p*=0.938).

After 5 minutes of drug administration, 124 patients (86.2%) in group-A and 74 patients (51.4%) in group B were not shivering and exhibited grade-0. A statistically significant difference was found between the two groups at 5 minutes (*p*<0.001) (Table-II).

Group-A received Pethidine 0.5 mg/kg while group-B received Ketamine 0.2 mg/kg. In group-A, effectiveness was noticed in 124 patients (86.2%), and in group B, effectiveness was seen in 74 patients (51.4%) (Table-III). A statistically significant difference

was found between the two groups [$p < 0.001$, Chi square value=40.404].

Table-II: Comparison between Pethidine and Ketamine for grade of shivering at 0 and 5 minutes.

Grade of Shivering at 0 Minute				
Grades of Shivering	Group-A (Pethidine 0.5 mg/kg) (n=144)	Group-B (Ketamine 0.2 mg/kg) (n=144)	X ² Value	p-value
Grade 0 (Treated)	0 (0%)	0 (0%)	0.129	0.938
Grade 1	30 (20.8%)	29 (20.2%)		
Grade 2	76 (52.8%)	79 (54.8%)		
Grade 3	38 (26.4%)	36 (25%)		
Grade of Shivering at 5 minutes				
Grade 0 (Treated)	124 (86.2%)	74 (51.4%)	42.262	<0.001
Grade 1	13 (9%)	33 (22.9%)		
Grade 2	3 (2%)	23 (16%)		
Grade 3	4 (2.8%)	14 (9.7%)		

Table-III: Effectiveness of drugs in both groups.

Effectiveness	Group-A Pethidine 0.5 mg/kg (n=144)	Group-B Ketamine 0.2 mg/kg (n=144)	X ² Value	p-value
Shivering Settled	124 (86.2%)	74 (51.4%)	40.404	<0.001
Shivering Not Settled	20 (13.8%)	70 (48.6%)		

DISCUSSION

Postoperative shivering primarily results from intraoperative hypothermia or the effects of anaesthetic agents. The most important cause is core to peripheral redistribution of heat due to vasodilation, mostly because of a decrease in sympathetic tone by almost all anaesthetic agents, spinal or epidural anaesthesia, the release of cytokines due to surgical procedure and postoperative pain.¹² General anaesthesia drugs also impair normal autonomic thermoregulatory mechanisms and decrease the shivering threshold.¹³ Decrease in core body temperature because of the cool operating room, open body cavities, use of unwarmed intravenous fluids and un-humidified gases are other main contributors.¹⁴

Postoperative complications are the primary cause of mortality and morbidity in surgical patients, making it a priority for anaesthetists to respond competently. Postoperative shivering is common in patients emerging from anaesthesia after vomiting and nausea.¹⁵ This condition is very inconvenient for patients recovering from surgical and anaesthesia

stress. Furthermore, it is poorly tolerated by patients with impaired cardiac or pulmonary functions.¹⁶ Therefore, hypothermia and shivering should be avoided and treated intra-operatively and postoperatively using a forced-air warming device, warming lights, heating blankets, intravenous fluid warmer, and warming of the operating room.¹³ If these non-pharmacological treatments are ineffectual, pharmacological treatment should not be delayed to avoid potentially deleterious side effects of shivering.²

Pethidine, a synthetic opioid and Ketamine, an anaesthetic agent & non-competitive antagonist of N-methyl D-aspartate (NMDA), are amongst the most efficacious drugs for shivering.⁹ Our study showed that the use of Pethidine (0.5 mg/kg) as compared to the Ketamine in patients (0.2 mg/kg) has a significant beneficial effect on postoperative shivering ($p < 0.001$). However, comparative studies of Pethidine vs Ketamine as an anti-shivering agent showed variability in results at the international level. Many studies compared the prophylactic use of different drugs to prevent shivering. However, we have preferred comparisons of drugs for the treatment of shivering to evade undue effects of pharmacological agents in those patients whose shivering is never going to develop.

A similar study conducted by Eydi *et al*, showed that administration of Ketamine could be associated with some undesirable complications (53.33% effectiveness) and conventional administration of Pethidine seems to be more logical and safer (70% effectiveness).¹¹ Luggya *et al*, in a prospective observational study for prevalence and treatment of post-spinal shivering in a tertiary hospital, showed that shivering was witnessed in only 22 patients out of 270 patients when administered intravenous Pethidine 25 mg, so it had effectively treated patients that got shivering.⁴ Some researchers like Ramalingaraju *et al*, compared the prophylactic effects of Ketamine and Pethidine for postoperative shivering and found that shivering was seen more commonly in the Ketamine group (14.9%) than in the Pethidine group (3.7%).^{17,18} Petskul *et al*, in a study, demonstrated that in the recovery room, no significant efficacy difference between low-dose Ketamine (0.25 mg/kg) and placebo in the prevention of postoperative shivering in patients who underwent Orthopaedic surgery was observed.⁷ Our study strongly advocated results by Kranke *et al*. They did systematic quantitative reviews of randomized controlled trials for pharmacological treatment of postoperative shivering, showing that after 5 minutes, the NNT of

Pethidine 25 mg was 1.3,¹⁹ and a meta-analysis of RCT by Park *et al*, for the efficacy spectrum of anti-shivering medications signifying that Pethidine is more effective (NNT: 2) than Ketamine (NNT: 3).²⁰

The studies were done by Tandon *et al*, Kose *et al*, Ayatollahi *et al*, found that Ketamine had shown more rapid onset and lower shivering grades than Pethidine when used for the treatment of shivering occurring postoperatively after general anaesthesia. However, the side effect profile restricts its practicality,²¹⁻²³ whereas, in our study, Pethidine was more effective in treating shivering postoperatively at 5 minutes after drug administration in recovery rooms.

Sayed demonstrated that in patients undergoing lower half surgery under spinal anaesthesia, there was no significant difference regarding the decreased incidence of shivering after prophylactic intravenous administration of 25mg Ketamine, 25mg Pethidine or 3mg Granisetron. 15% of patients in each group developed shivering within 60 minutes of respective drug administration.²⁴

Zabetian *et al*, in a comparative study on different doses of Ketamine and Pethidine for prevention of shivering during and after spinal anaesthesia at cesarean section, found that the difference in intensity of shivering between 0.3 mg/kg Ketamine, 0.15 mg/kg Ketamine and 25mg Pethidine was insignificant at 5, 10, 15, 30 and 45 minutes.¹⁰ Hasannasab *et al*, observed that 20mg Pethidine, 0.25 mg/kg Ketamine, and 0.25 mg/kg Doxapram are equivalently effective in avoiding postoperative shivering.⁵ No comparative study between these two drugs has been done in Pakistan previously.

CONCLUSION

Considering the results of our study and after comparing the grades and frequency of shivering following administration of drugs in studied groups, Pethidine 0.5 mg/kg proves to be the ideal choice for treatment of postoperative shivering compared to Ketamine 0.2 mg/kg.

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Conflict of Interest: None.

Author's Contribution

MUF: Principal investigator, conception, design, data collection, analysis, interpretation of data, FY: Design, analysis, interpretation, intellectual, MA: intellectual, analysis, RASK: Supervisor, intellectual, analysis, revising, AK:, AA: intellectual contribution.

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