

## To Compare the Effectiveness Of Low Dose Intravenous Ketamine Versus Pethidine For Postoperative Shivering In Surgical Patients Under General Anesthesia: A Prospective Cohort Study

Research Article

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### Abstract

**Background:** Postanesthesia shivering is one of the potential complications of anesthesia which may increase patient morbidity. Various methods had been employed to control postoperative shivering. This study assessed the effectiveness of prophylactic low dose intravenous ketamine and pethidine for postoperative shivering after general anesthesia.

**Methods and Materials:** This prospective cohort study recruited 76 ASA I and II patients aged 18-65 years old and underwent elective surgery under general anesthesia. The patients were grouped by blinded anesthetist to take either ketamine 0.5mg/kg or pethidine 0.5 mg/kg 20 minutes before completion of the surgery. The incidence and severity of postoperative shivering were compared between the two groups every 10 minutes until one hour postoperatively. The side effects of the study drugs were also compared between the two groups in the recovery room. Categorical data were analyzed with the Chi-Square test. Parametric and non-parametric data between the groups were analyzed using independent samples t-test and Mann-Whitney U test respectively. A p-value of <0.05 was considered statistically significant.

**Results:** The incidence of shivering between the ketamine and pethidine groups was 11 (28.2%) and 14 (35.9%) respectively ( $p=0.467$ ). The severity of shivering was not significantly different between the two groups ( $p=0.893$ ). The occurrence of nausea and vomiting and sedation attributed to the drugs was significantly less in the ketamine group ( $p<0.05$ ). PACU stay duration and occurrence of hallucination among the groups were comparable. ( $p>0.05$ )

**Conclusion and Recommendation:** This study revealed administering low dose IV ketamine (0.5mg/kg) 20 minutes before completion of surgery reduced postoperative shivering as effectively as pethidine. The study also showed clinically better outcomes in favor of ketamine since it was associated with fewer side effects. Thus, we recommend low dose IV ketamine 20 minutes before completion of surgery under general anesthesia to prevent postoperative shivering.

**Keywords:** Ketamine; Pethidine; General Anesthesia; Postoperative Shivering; Elective Surgery.

**Abbreviations:** ASA: American Society of Anesthesiologists; BMI: Body Mass Index; CO<sub>2</sub>: Carbon Dioxide; ECG: Electrocardiography; GA: General Anesthesia; IV: Intravenous; NMDA: N-methyl-D aspartate; PACU: Postanesthesia Care Unit; PAS: Post-Anesthesia Shivering.

### Introduction

Shivering after surgery under general anesthesia is a very common problem with the incidence of 65% but varies in severity. It can sometimes cause a great deal of discomfort in surgical patients recovering from general anesthesia [1, 2]. Moreover, it may have deleterious sequelae in the post-operative period I.e. increased oxygen consumption, increased CO<sub>2</sub> production, increased risk

of postoperative hypoxemia, increased catecholamine release, increased cardiac workload and risk of perioperative myocardial ischemia, increased recovery room stay, and disturbing the reading of monitors [3]. The problem is more pronounced in developing countries where surgery is undertaken in a poorly equipped and devoid of a perioperative temperature control system and poorly practiced modern anesthetics I.e. predominantly using volatile anesthetics [4, 5].

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While there were different pharmacological and nonpharmacological methods tried in the past to control shivering that occurs intraoperatively and postoperatively, no novel methods and treatment modalities discovered so far [6]. Pharmacological agents used to prevent or treat the post-operative shivering, include alfentanil, sufentanil, ketanserin, physostigmine, nefopam, urapidil, doxapram, tramadol, nalbuphine, and pethidine, but the ideal drug for this query has become questionable [7]. Among these drugs, pethidine is the most effective drug but disadvantages like nausea, vomiting, hallucination, and respiratory depression precludes its utilization [8, 9, 18].

At several levels, N-methyl-d-aspartate receptor antagonists are likely to modulate thermoregulation. Ketamine, the NMDA receptor competitive antagonist, has different characteristics such as cerebral vasodilatation, induction of relaxation of bronchial smooth muscle, amnesia, ability to increase intracranial pressure, cause transient, and marked increase of blood pressure by sympathetic system stimulation, and analgesia. Ketamine can likely control shivering, as a prophylactic agent [4, 9, 10]. This study aimed to compare the effectiveness of prophylactic low dose ketamine and pethidine as a way of preventing post-operative shivering after general anesthesia.

## Methodology

After obtaining ethical approval from the institutional ethics committee of Addis Ababa University College of health sciences, a prospective cohort study was conducted from January 01 to April 30, 2018, at Tikur Anbessa specialized hospital, Addis Ababa Ethiopia. The study involved 76 ASA I and II patients aged 18-65 years old undergoing elective surgery under general anesthesia. Sample size was calculated to compare two proportions based on the following assumptions: significance level 5% ( $\alpha = 0.05$ ), and power of study ( $1 - \beta$ ) of 80%. From previous study, the effectiveness of pethidine 0.5mg/kg and ketamine 0.5 mg/kg in preventing postoperative shivering was found to be 88.9% and 62.2% respectively (Zabareh SMHT, et al. 2012) thus it's computed as follows:

$$n_1 = n_2 = \frac{p_1(1 - p_1) + p_2(1 - p_2) \times (z_{\alpha} + z_{\beta})^2}{(p_1 - p_2)^2}$$

$$= \frac{(0.889)(0.111) + (0.622)(0.378) \times 7.84}{(0.889 - 0.622)^2} = 37 \text{ per each group}$$

Where,

- $n_1$  = number of clients to take pethidine
- $n_2$  = number of clients to taken ketamine
- $Z$  = 95% confidence interval = 1.96
- $F(\alpha, \beta)$  = the power function at 80% = 7.84
- $P_1$  = Efficacy in percentage for pethidine (88.9%),  $Q_1$  is  $1 - P_1$  (11.1%)
- $P_2$  = Efficacy in percentage for ketamine (62.2%),  $Q_2$  is  $1 - P_2$  (37.8%)

By considering a contingency of 5%, the study involved 39 individuals. Thus, the total sample for both groups was  $39 \times 2 = 78$ . Two participants were excluded because of loss to follow up. Thus, 76 participants completed the study.

The verbal consent was obtained from each participant to be involved in the study. The participants were selected using a systematic random sampling technique.

Patients induced with ketamine, BMI >30, thyrotoxicosis, psychiatric problems, patients taking blood transfusion, hypertensive patients, and convulsion were excluded from the study. The anesthetic management of patients in both groups was according to the hospital's routine practice guidelines. Anesthesia was induced with propofol 2mg/kg, morphine 0.1mg/kg and vecuronium 0.1 mg/kg to facilitate tracheal intubation. Anesthesia was maintained with intermittent bolus vecuronium 0.1mg/kg and halothane 1-1.5%. In all patients, no active warming had been utilized throughout the procedure. Patients were monitored using ASA standard monitors. At about 20 minutes to complete the surgery, patients were grouped to take either ketamine 0.5mg/kg IV or pethidine 0.5mg/kg IV as prophylaxis for postoperative shivering by the anesthetist unaware about the study drugs. At the end of the surgery, the trachea was extubated after successful antagonism of neuromuscular blockade with neostigmine 0.04mg/kg and atropine 0.02mg/kg.

Patients were transferred to PACU once adequate depth and rate of respiration ensured, and respond to commands. Patients were monitored as per guidelines in the recovery room. Moreover, patients were observed for the occurrence and severity of shivering and side effects of the study drugs after arrival into PACU. The severity of shivering was evaluated by a 5-grade scale. (Grade 0: no shivering, grade I: peripheral vasoconstriction, grade II: shivering involving one muscle group only, grade III: shivering in more than one muscle group, and grade IV: shivering involving whole body). Drug side effects like hallucination, sedation, nausea, and vomiting were observed in the postoperative period.

The data was analyzed using SPSS version 20 after it is cleaned and coded. Independent samples t-test and Mann-Whitney U test were used for quantitative data analysis that was distributed normally and non-normally respectively. A Chi-square test was used to analyze categorical data. Shapiro Wilks and Levene's tests were used to checking the normality of data and homogeneity of variances respectively. A P-value of less than 0.05 was considered a statistically significant difference in observation.

## Results

A total of seventy-six ASA I and II patients were enrolled in the study and were grouped into ketamine and pethidine group each group containing 38 patients to compare the effectiveness of low dose ketamine and pethidine as a way of preventing postoperative shivering. The comparison of demographic and operative characteristics including age, sex, height, weight, BMI, and ASA showed no significant difference between the two groups. (Table 1)

The number of shivering patients in ketamine and pethidine groups was 11 (29%) and 14 (36.8%) respectively ( $p = 0.467$ ). The severity of shivering among the two groups was compared and no statistically significant difference was observed ( $p > 0.05$ ). (Figure 1)

The comparison of intraoperative factors such as type and duration of surgery, amount of blood loss, and total fluid adminis-

tered has shown no statistically significant difference among the groups. ( $p > 0.05$ ) (Table 2)

The patients were observed for possible side effects such as sedation, hallucination, nausea, and vomiting, and duration of PACU stay. (Figure 2)

### Discussions

Postoperative shivering had remained one of the common adverse events in the patients recovering from general anesthesia. Furthermore, it is associated with a major deal of discomfort to both the patients and the medical care team. This prospective observational study compared the effectiveness of prophylactic intravenous ketamine 0.5mg/kg and pethidine 0.5mg/kg in elective surgical patients under general anesthesia.

The antishivering effect of pethidine was suggested by several reports. Its antishivering effect pertains to the  $\kappa$ -opioid receptor

but not due to  $\mu$ -receptor-mediated [9, 11, 12]. Even though, it had been a novel antishivering drug, side effects related to pethidine preclude its utilization in some situations [13].

The preventive effect of ketamine for postoperative shivering was realized in many studies. However, its mechanism of action became difficult to predict due to the pharmacological complexity of the drug. The possible speculation for its anti-shivering effect would be its action on the thermoregulatory center via NMDA antagonism. Inhibition of NE reuptake at postganglionic fiber by ketamine induces peripheral vasoconstriction which in turn decreases core to peripheral redistribution of heat [11, 12, 14].

In this study, demographic factors like age, gender, weight, height, ASA physical status, and BMI were all found to be comparable between the two groups; the type and duration of surgery, amount of blood loss and total fluid intake which were considered as risk factors for perioperative hypothermia and shivering [15], were all comparable between the two groups ( $p > 0.05$ ).

**Table 1. Demographic and operative characteristics.**

	Ketamine group	Pethidine group	P-value
Age	42.95 ± 11.82	41.74 ± 12.49	0.663
Gender(M/F)	20/19	21/18	0.821
Height	166.15±5.52	167.36 ± 5.80	0.35
Weight	62.23 ± 8.31	64.26 ± 5.48	0.208
BMI	22.47 ± 2.36	23.02 ± 1.17	0.196
ASA(I/II)	24/15	21/18	0.492

**Table 2. Intraoperative exposure variables in elective surgical patients under general anesthesia.**

variables	Ketamine group	Pethidine group	P-value
Types of surgery			
Abdominal surgery	14	12	
Gynecologic surgery	10	12	0.932
Orthopedic surgery	10	11	
Urologic surgery	5	4	
Duration of surgery(minute)	124.51 ± 24.27	130.25 ± 30.45	0.360
Total fluid given(ml)	2425.64 ± 619.73	2450 ± 672.68	0.868

Type of surgery presented in numbers, others in mean ± SD.

**Table 3. The side effects of study drugs in elective surgical patients under general anesthesia.**

	Ketamine group	Pethidine group	P-value
Sedation			
Yes	6(7.9%)	16(21%)	0.012
No	32(92.1%)	11(79%)	
PACU stay (minutes)	48.85±6.73	50.13±5.90	0.374
Nausea and vomiting	1	7	0.025
Hallucination	3	1	0.305

Sedation, nausea and vomiting, and hallucination are described in numbers, PACU stay time described in mean+ SD. SD: standard deviation

Figure 1. Bar graphs displaying the severity of postoperative shivering in elective surgical patients under general anesthesia.

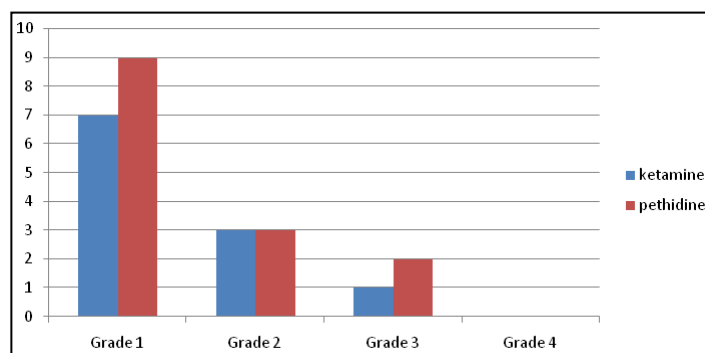
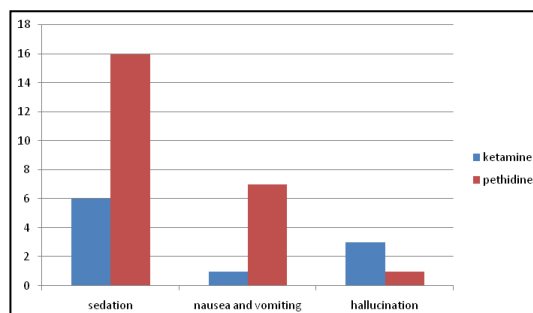


Figure 2. Bar graphs showing side-effects among elective surgical patients under general anesthesia.



In this study, the overall incidence of postoperative shivering was 32.1%. This rate is higher than the report from the study conducted in Isfahan University of medical sciences, Iran by Zabareh SMHT et al. In their study, the overall shivering rate was 26.7% which is smaller than the rate of our study [12]. The cause for this might be a variation in intraoperative and postoperative patient management. Another speculation could be Intraoperative use of fentanyl which also has an anti-shivering effect, and higher operation room ambient temperature in their study.

In this study, the number of shivering patients was 11(28.2%) and 14(35.9%),  $p=0.467$  for ketamine, and pethidine group respectively. Although the difference was statistically insignificant, it seems practically a better outcome in favor of ketamine. This finding is in line with the study conducted in India by Dar AM, et al. Their study showed no statistically significant difference found between ketamine and pethidine groups ( $p>0.05$ ) [16]. This might be due to the utilization of the same dose of the study drugs. Another study conducted in Mashhad, Iran by Masomeh et al also reported pethidine and ketamine can similarly reduce post-operative shivering [17]. Our study result also supported by a study in Tabriz University of Medical Sciences, Iran by Eydi M. et al in 2014 [18]. The result of their study showed that ketamine and pethidine are both equally effective in reducing postoperative shivering. This could be due to a similar study design. Also, another study, conducted by Ayatollahi V et al in Iran had reported a similar finding to our study. Their study reported prophylactic use of low doses of intravenous ketamine (0.3 or 0.5 mg/kg) was found to be effective to prevent postanesthetic shivering. However, administration of 0.3 mg/kg ketamine lowered the rate of hallucination as compared with 0.5 mg/kg. [13]. This might be related to different drug responses. A prospective RCT conducted in Isfahan University of medical sciences, Iran by Zabareh SMHT et al reported a contradictory finding in favor of pethidine. They said pethidine seems to be the most appropriate choice for pre-

venting postoperative shivering [12]. The difference in the study design could have contributed to this discrepancy.

Another prospective randomized study conducted by Emine Arzu et al in Hacettepe University, Turkey showed ketamine in doses of 0.5-0.75 mg/kg had better reduced post-operative shivering than pethidine. But ketamine 0.75 mg/kg associated with more hallucination [19]. This might be caused by a higher dose of ketamine. Another contradictory result to our finding was reported by the study conducted in Motahari Hospital in Jahrom (Iran), by Zabetian H, et al in 2016 [20]. The possible explanation could be due to the usage of a small dose of ketamine than this study.

The severity of postoperative shivering was compared between the two groups and the difference was not statistically significant ( $p=0.874$ ). A randomized double-blind study conducted by Dar AM, et al showed similar findings to this study. The number of patients with grade 1 shivering was 7 and 9 in ketamine and pethidine group respectively while 3 patients in each group developed grade shivering. This result is in line with the prospective RCT conducted by Masomeh et al. [17] In their study, while only one patient in ketamine group developed grade 1 shivering, no patient has developed either grade 2 or 3 shiverings. But their finding for the pethidine group was similar to the result of this study. This could be due to less dose pethidine used to prevent postoperative shivering. This study was also supported by a randomized study conducted by Dar AM et al, which showed the number of patients with grade 1 and 2 shivering were 4 and 3 in both ketamine and pethidine groups respectively ( $p>0.05$ ).

In this study, side effects like hallucination, nausea, and vomiting, duration of PACU stay, and sedation associated with the study drugs were compared between the two groups.

The number of sedated patients was significantly higher in pethidine than ketamine group: 6(15.8%) versus 16(42.1%) for keta-



mine and pethidine group respectively,  $p=0.012$ . This could be due to differences in the duration of elimination for ketamine and pethidine. Another difference might be due to the combined effects of pethidine with intraoperative morphine, inhalational anesthetics, and perioperative hypothermia.

In this study, nausea and vomiting were observed among the groups and found to be significantly different,  $p=0.025$ . The possible explanation could be opioid-induced activation of the chemoreceptor trigger zone.

PACU stay time between the groups was found to be comparable ( $48.85 \pm 6.73$  and  $50.13 \pm 5.90$  minutes for ketamine and pethidine groups respectively,  $p=0.374$ ). The result of a study conducted in Iran by Ayatollahi et al. revealed the duration of PACU stay for ketamine and pethidine group was  $64.50 \pm 1.43$  minutes and  $56.67 \pm 1.27$  minutes respectively. (14) In the same study, the length of PACU stay was  $49.37 \pm 1.22$  minutes and  $43.10 \pm 1.60$  minutes in those who took ketamine  $0.3 \text{ mg/kg}$  and control group. Thus, PACU stay time in previous groups was slightly long. The reason could be attributed to the higher dose of study drugs.

This is the first study in our country; thus it could be an important source of information for clinical researchers. However, the lack of randomization and control for room temperature and the temperature of intravenous fluids in the institution might be the limitation of this study.

## Conclusion

This study has proved prophylactic low dose ketamine could prevent post-operative shivering as effectively as pethidine and associated with fewer side effects. We recommend using ketamine  $0.5 \text{ mg/kg}$  20 minutes before the end of operation to prevent postoperative shivering. We also recommend ketamine because it is easily available in the operation room and cost-effective.

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