

Original Article**Comparison of prophylactic use of meperidine and two low doses of ketamine for prevention of post-anesthetic shivering: A randomized double-blind placebo controlled trial***

Vida Ayatollahi¹, Mohammad Reza Hajiesmaeil², Shekoufeh Behdad¹,
Mohammad Gholipur³, Hamid Reza Abbasi¹

Abstract

BACKGROUND: Postanesthetic shivering is one of the most common complications of anesthesia. We compared the efficacy of meperidine and two low doses of ketamine with placebo to prevent postanesthetic shivering after general anesthesia.

METHODS: This was a prospective, randomized double-blind placebo controlled clinical trial involving 120 ASA I-II patients aging 20-50 years, undergoing endoscopic sinus surgery with general anesthesia. Patients were randomly allocated to receive meperidine 0.4 mg/kg (Group M, n = 30), ketamine 0.3 mg/kg (Group K₁, n = 30), ketamine 0.5 mg/kg (Group K₂, n = 30), or normal saline (Group N, n = 30) 20 minutes before completion of the surgery. Tympanic temperature, blood pressure, and heart rate were measured before and immediately after induction of anesthesia, 30 minutes after induction, and before administration of the study drugs. The drugs were prepared and diluted to a volume of 2 ml and presented as coded syringes. An investigator, blinded to the groups, graded postanesthetic shivering using a four-point scale. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) Windows version 16. A p-value < 0.05 was considered statistically significant.

RESULTS: Patient characteristics of the four groups were similar. The number of patients with observed shivering in groups was 0, 3, 1, and 9 in Groups M, K₁, K₂ and N, respectively. The difference between groups M, K₁, and K₂ with Group N was statistically significant. However, differences between groups M and K₁, M and K₂, and K₁ and K₂ were not significant. The number of patients with a shivering score of 2 or 3 was higher in Group N compared with other groups.

CONCLUSIONS: 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.

KEYWORDS: Postanesthetic Shivering, Meperidine, Ketamine.

J Res Med Sci 2011; 16(10): 1340-1346

Postanesthetic shivering is a very unpleasant experience occurring in 5-65% of patients recovering from general anesthesia and 57% of volunteers undergoing regional anesthesia.^{1, 2} It causes physiological stress resulting in increased oxygen consump-

tion, carbon dioxide production, cardiac output, intraocular and intracranial pressure and other complications of sympathetic stimulation.^{1, 3-4} Thus, prevention and treatment of postanesthetic shivering is an important aspect of patient care. Although various drugs includ-

* This article resulted from project NO. 2071.

1- Associate Professor, Department of Anesthesiology, School of Medicine, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran.

2- Resident, Department of Anesthesiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

3- Anesthesiologist, Department of Anesthesiology, School of Medicine, Kermanshah University of Medical Sciences and Health Services, Kermanshah, Iran.

Corresponding Author: Shekoufeh Behdad

E-mail: drbehdad@yahoo.com

ing ketamine,^{1,7} meperidine,^{1,3, 8} alfentanil,⁸ tramadol,⁹ magnesium sulfate,¹⁰ ondansetron,¹¹ dolasetron,¹² and physostigmine¹³ have been used to treat or prevent the problem, the ideal drug has not yet been found.

Meperidine has shown to be one of the most effective drugs.^{1,3, 8, 14} However, it has some disadvantages such as respiratory depression especially in patients who had previously used opioid or anesthetics, nausea, vomiting, and hallucination.^{1, 8}

Ketamine, a competitive N-methyl-d-aspartate receptor antagonist, can probably control shivering.^{1, 7} Ketamine 0.5–0.75 mg/kg is more rapid than meperidine (25 mg) for the treatment of postanesthetic shivering.³ Ketamine 0.25 mg/kg in combination with midazolam 37.5 µg/kg is effective for the prevention of shivering in regional anesthesia.²

Based on our knowledge, there has been no study regarding the use of a low dose of ketamine (less than 0.5 mg/kg) as the sole agent for treatment or prevention of postanesthetic shivering in general anesthesia. Therefore, this study was designed to compare the efficacy of intravenous ketamine at a lower dose than previously reported doses (0.3 mg/kg) with placebo, ketamine 0.5 mg/kg, and meperidine 0.4 mg/kg for prevention of postanesthetic shivering after general anesthesia.

Methods

This randomized double blind clinical trial included 120 patients of both genders aged 20-50 years from March 29006 to January 2009. All patients were American Society of Anesthesiologist class I or II and underwent endoscopic sinus surgery under general anesthesia. Before the study was performed, it was approved by the Ethics Committee and written informed consents were obtained from all patients. Patients with hypothyroidism, hyperthyroidism, hypertension, cardiopulmonary disease, psychological disorders, body mass index > 30 kg/m², a history of convulsions or addictions, multiple allergies, duration of anesthesia < 1 hour or >3 hours, initial tympanic temperature > 38 °C or < 36.5 °C, and those who received

blood products or metoclopramide were excluded from the study.

Patients were randomly (using table of random numbers) allocated to receive normal saline (Group N, n = 30), meperidine 0.4 mg/kg (Group M, n = 30), ketamine 0.3 mg/kg (Group K₁, n = 30) or ketamine 0.5 mg/kg (Group K₂, n = 30) intravenously 20 minute before the end of surgery. The study drugs were diluted to a volume of 2 ml and presented as coded syringes by an anesthetist who was not involved in the management of patients or in the grading of patients' shivering. There was a 1:1 ratio for randomization. The patients and the rater were blind to the groups.

Heart rate, non-invasive systolic blood pressure and oxygen saturation were monitored during the surgery and automatically recorded every 10 minutes. The temperature of intravenous (IV) fluids administered was equal. Tympanic membrane temperature was measured using a digital ear thermometer (an aural canal thermometer, OMRON 510, Germany) and recorded before anesthesia, immediately after induction of anesthesia, 30 minutes after induction, and before administration of the study drugs. In the operating room, patients were covered with a cotton blanket.

The ambient temperature, in the operating and recovery rooms, was measured by a wall thermometer and maintained at 23 ± 0.5°C.

In all patients, the anesthesia was induced with fentanyl 1.5 µg/kg IV, propofol 2 mg/kg, and pancuronium 0.1 mg/kg. Anesthesia was maintained with nitrous oxide 70% in oxygen and isoflurane 1-1.5%. Repeated doses of pancuronium 0.03 mg/kg were given when train-of-four (TOF) visible twitches were ≥ 2.

Approximately 20 minutes before completion of the surgery, patients were randomly assigned to receive the study drug using a simple randomization method. Residual neuromuscular blockade was reversed using neostigmine 0.03 mg/kg and atropine 0.01 mg/kg. Then, the trachea was extubated. The duration of the surgery, anesthesia and Post-Anesthesia Care Unit (PACU) stay were recorded.

In the recovery room, the patients were monitored and covered with a cotton blanket. No patient was warmed actively and all patients received oxygen 4 lit/min via a face mask.

The shivering was graded using a four-point scale (0 = no shivering, 1 = mild fasciculation of face or neck, 2 = visible tremor involving more than one muscle group, 3 = gross muscular activity involving the entire body).

An anesthetist unaware of the study observed the patient for shivering, nausea, vomiting, hallucination, pain, and time of first analgesia request after admission to the recovery room. The possible side-effects of the study drugs including nausea, vomiting, hypotension or hypertension (< or > 30% baseline), tachycardia, respiratory problems, oxygen desaturation, and hallucination were recorded. Patients with shivering were treated with meperidine 20 mg IV if the shivering grade was \geq 2. Postoperative pain in the endoscopic sinus surgery was assessed by visual analogue scale (VAS) 60 minutes postoperatively and treated with morphine 0.05 mg/kg IV if VAS \geq 3 in the recovery room. If tympanic temperature was < 36°C active warming was used. Postoperative analgesia required and time to first analgesia required were recorded. Moreover, sedation level was assessed using The Richmond Agitation-Sedation Scale (RASS) 30 minutes after PACU entrance. PACU stay time

(min) was also assessed.

The sample size was calculated for one way analysis of variance with four levels and a power of 80% which indicated a minimum of 28 cases in each groups.

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) Windows version 15. Chi-square, Kruskal-Wallis, and Mann-Whitney tests were used where they were appropriate. A p-value < 0.05 was considered statistically significant. The difference between the shivering grades in different groups was assessed using Kruskal-Wallis test. The difference between the numbers of patients with observed shivering in every two groups was evaluated using Dunn's test (GraphPad Prism software). The difference between the number of patients with nausea, hallucination and postanesthetic shivering in the recovery room was analyzed using chi-square test. We used repeated measure analysis of variance (ANOVA) for analysis of repeated continuous variables.

Results

The mean (mean \pm SD) of age, weight, height, duration of surgery, duration of anesthesia, baseline tympanic temperature and distribution of sex and American Society of Anesthesiologist classes were similar in all the groups (Table 1).

Table 1. Patient characteristics

	Group M (n = 30)	Group K ₁ (n = 30)	Group K ₂ (n = 30)	Group N (n = 30)
Age (years)	41 \pm 11.5	38.5 \pm 15.5	42.3 \pm 13.1	39.1 \pm 10.1
Weight (kg)	67.9 \pm 6.8	70.1 \pm 8.2	68.6 \pm 9.3	65.3 \pm 6.4
Height (cm)	160.3 \pm 9.2	165.1 \pm 5.1	163.5 \pm 8.2	158.8 \pm 6.4
Sex (f/m)	13/17	12/18	12/18	17/13
ASA* physical status (I/II)	25/5	27/3	28/2	26/4
Baseline temperature (°C)	36.57 \pm 0.45	36.64 \pm 0.31	36.56 \pm 0.18	36.68 \pm 0.4
Anesthesia time (min)	126 \pm 36.9	119.4 \pm 39.2	131.2 \pm 12.1	120.2 \pm 37.4
Surgery time (min)	140.37 \pm 3.38	140.23 \pm 3.13	139.60 \pm 3.31	139.93 \pm 3.04

Data are presented as number of patients or mean \pm SD.

Age, weight, height, duration of surgery, duration of anesthesia, baseline tympanic temperature and distribution of sex and American Society of Anesthesiologist classes were similar in all the groups (p < 0.05).

* ASA: American Society of Anesthesiologists.

The number of patients with postanesthetic shivering in the recovery room and their grades were significantly less in Groups M, K₁ and K₂ than in group N ($p = 0.001$ and $p = 0.001$, respectively) Women in all of groups (except Group M) had higher incidences and grades of shivering, but the differences were not significant ($p = 0.288$).

The number of patients with observed shivering in different groups was 0, 3 (grade I = 1, II = 1 and III = 1), 1 (grade I = 1), and 9 (grade I = 1, II = 4 and III = 4) in Groups M, K₁, K₂, and N, respectively (Table 2). None of the patients required a second dose of meperidine within a 60-minute period.

Repeated measure ANOVA did not reveal any significant differences between the groups in heart rate, non-invasive systolic blood pressure, oxygen saturation, and tympanic membrane temperature throughout the study period.

Postoperative pain (VAS), postoperative analgesia required and time to first analgesia required were significantly different between the study groups. In addition, sedation level (RASS) and PACU stay time were significantly different between the study groups, as well (Table 3).

Five patients in Group M, 4 in Group K₁, 7 in Group K₂ and 4 in Group N had nausea. The difference between the groups was not statistically significant ($p = 0.696$) (Table 3). Among

all patients, only three in Group K₂ had hallucination. The difference between Group K₂ and other groups was statistically significant ($p = 0.026$) (Table 4). None of the patients had vomiting, tachycardia, hypotension or hypertension, respiratory problems, or oxygen desaturation (Table 4).

Discussion

A number of recent studies have focused on the prophylactic use of ketamine for prevention and treatment of postanesthetic shivering. The present study is a dose finding study in which we studied the efficacy of ketamine at a lower dose than previously reported doses (0.3 mg/kg) as compared with meperidine, placebo, and ketamine 0.5 mg/kg. Similar to previous studies,¹⁻⁷ ketamine was shown to prevent shivering without producing hemodynamic alterations in patients undergoing regional or general anesthesia in our study.

Dal et al. compared placebo, meperidine and ketamine 0.5 mg/kg for prevention of shivering after general anesthesia and found ketamine 0.5 mg/kg to be effective. In contrast to a 10% hallucination which was observed in our study at the same dose and without a clear cause, no hallucination was noticed in their study.¹ The reason might be different drugs used for induction and maintenance of anesthesia, i.e. pancuronium versus vecuronium, and isoflurane versus sevoflurane.

Table 2. Postoperative shivering

Shivering score	Group M (n = 30)	Group K ₁ (n = 30)	Group K ₂ (n = 30)	Group N (n = 30)	Total
0	30 (100)	27 (90.0)	29 (96.7)	21 (70.0)	107(89.2)
1	(0.0)	1 (3.33)	1 (3.33)	1 (3.33)	3
2	(0.0)	1 (3.33)	0 (0.0)	4 (13.3)	5
3	(0.0)	1 (3.33)	0 (0.0)	4 (13.3)	5
Total	0	3	1	9	13

The data is represented as n (%).

The differences of the number of patients with observed shivering between groups with Kruskal-Wallis test was significant ($p = 0.0006$). The differences between Groups M and N, and K₂ and N, with Dunn's test (GraphPad Prism software), were statistically significant ($p < 0.001$ and $p < 0.01$, respectively).

Table 3. Postoperative pain

	Group M (n = 30)	Group K ₁ (n = 30)	Group K ₂ (n = 30)	Group N (n = 30)
Postoperative pain (VAS)*	0.5 ± 0.51	2.5 ± 0.51	1.5 ± 0.51	2.5 ± 0.51
Postoperative analgesia required (n)	–	2	1	2
Time to first analgesia required (min)	–	52.5	45	50

Postoperative pain, postoperative analgesia required and time to first analgesia required were significantly different between the study groups ($p < 0.001$).

* VAS: Visual Analog Scale

However, Sharma and Thakur reported that ketamine IV 0.5 mg/kg was effective in the treatment of shivering after general and regional anesthesia. In their study, only two patients had hallucination and four patients had delirium that was similar to our study.⁷

Honarmand and Safavi compared the efficacy of prophylactic saline, midazolam 75 µg/kg, ketamine 0.5 mg/kg, and midazolam 37.5 µg/kg combined with ketamine 0.25 mg/kg. They reported that core body temperature was reduced by premedication with IV midazolam, while it was increased with ketamine. In contrast, core body temperature did not show any changes when the two drugs were combined. In their study, prophylactic use of ketamine combined with midazolam was more effective than ketamine or midazolam IV in prevention of shivering in patients undergoing regional anesthesia.²

Kose et al. reported ketamine 0.5 and 0.75 mg/kg to be effective and more rapid than meperidine 25 mg for the treatment of postanesthetic shivering but some side effects in-

cluding nystagmus and a feeling like "walking in space" were seen.³

Zahra et al. found that the use of ketamine 1 mg/kg intramuscularly (IM) to be effective in preventing postanesthetic shivering in children.⁴

Sagir et al. compared placebo, ketamine 0.5 mg/kg, granisetron 3 mg and ketamine 0.25 mg/kg combined with granisetron 1.5 mg for prevention of shivering caused by regional anesthesia. They realized that after 15 minutes, in the group where ketamine 0.5 mg/kg was administered shivering was not observed in any patient. They found it significantly different compared with other groups.⁵

Norouzi et al. found using prophylactic 0.25 and 0.5 mg/kg ketamine as effective in preventing postanesthetic shivering with a better response observed with 0.25 mg/kg dosage.¹⁵

Piper et al. used (S)-ketamine for postoperative analgesia and found it to reduce not only postanesthetic shivering, but also postoperative nausea and vomiting.⁶

Table 4. Recovery characteristics

	Group M (n = 30)	Group K ₁ (n = 30)	Group K ₂ (n = 30)	Group N (n = 30)
Sedation level (RASS)*	-0.43 ± 1.14	0.27 ± 0.83	-1.00 ± 0.69	0.00 ± 0.69
PACU** stay time (min)	56.67 ± 1.27	49.37 ± 1.22	64.50 ± 1.43	43.10 ± 1.60
Nausea (n) (%)	5(16.7)	4(13.3)	7(23.3)	4(13.3)
Vomiting (n) (%)	–	–	–	–
Hallucination (n) (%)	–	–	3(10.0)	–

Sedation level and PACU stay time were significantly different between the study groups ($p < 0.001$). The differences in nausea and hallucination were not statistically significant between the groups ($p = 0.696$ and $p = 0.026$, respectively).

* RASS: Richmond Agitation–Sedation Scale

** PACU: Post-Anesthesia Care Unit

Sharma and Thakur reported that ketamine IV 0.5 mg/kg was effective in the treatment of shivering after general and regional anesthesia.⁷ In their study 10% of patients with 0.5 mg/kg ketamine had hallucination, too in our study. Gecaj-Gashi et al. used ketamine 0.5 mg/kg for prevention of postanesthetic shivering and confirmed our results.¹⁶ However, its mechanism of action is not completely understood and it may act directly on the thermoregulatory center or via opioid receptors.¹

A limitation of this study was not measuring peripheral temperature. It is suggested to collect peripheral temperature in the future studies and analyze its changes.

Conclusions

In conclusion, prophylactic use of low doses

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 resulted in lower rates of hallucination compared with 0.5 mg/kg ketamine.

Acknowledgement

This project was supported by the Research Deputy, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences and Health services, Yazd, Iran. The authors are grateful to in the staff members of otolaryngology operating room in Shahid Sadoughi Hospital, Yazd University of Medical Sciences.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

VA, SB, MG, MRHE and HA coordinated the study, carried out the design, analyzed the data, and prepared the manuscript. All the authors have read and approved the content of the manuscript.

References

1. Dal D, Kose A, Honca M, Akinci SB, Basgul E, Aypar U. Efficacy of prophylactic ketamine in preventing postoperative shivering. *Br J Anaesth* 2005; 95(2): 189-92.
2. Honarmand A, Safavi MR. Comparison of prophylactic use of midazolam, ketamine, and ketamine plus midazolam for prevention of shivering during regional anaesthesia: a randomized double-blind placebo controlled trial. *Br J Anaesth* 2008; 101(4): 557-62.
3. Kose EA, Dal D, Akinci SB, Saricaoglu F, Aypar U. The efficacy of ketamine for the treatment of postoperative shivering. *Anesth Analg* 2008; 106(1): 120-2
4. Zahra FA, Abudallah HM, Shabana RI, Abdulmageed WM, Abdulrazik SI, Nassar AM. Intramuscular ketamine for prevention of postanesthesia shivering in children. *Saudi Med J* 2008; 29(9): 1255-9.
5. Sagir O, Gulhas N, Toprak H, Yucel A, Begec Z, Ersoy O. Control of shivering during regional anaesthesia: prophylactic ketamine and granisetron. *Acta Anaesthesiol Scand* 2007; 51(1): 44-9.
6. Piper SN, Beschmann RB, Mengistu A, Maleck WH, Boldt J, Rohm KD. Postoperative analgosedation with S(+)-ketamine decreases the incidences of postanesthetic shivering and nausea and vomiting after cardiac surgery. *Med Sci Monit* 2008; 14(12): I59-I65.
7. Sharma DR, Thakur JR. Ketamine and shivering. *Anaesthesia* 1990; 45(3): 252-3.
8. Wrench IJ, Cavill G, Ward JE, Crossley AW. Comparison between alfentanil, pethidine and placebo in the treatment of post-anaesthetic shivering. *Br J Anaesth* 1997; 79(4): 541-2.
9. Heid F, Grimm U, Roth W, Piepho T, Kerz T, Jage J. Intraoperative tramadol reduces shivering but not pain after remifentanil-isoflurane general anaesthesia. A placebo-controlled, double-blind trial. *Eur J Anaesthesiol* 2008; 25(6): 468-72.
10. Wadhwa A, Sengupta P, Durrani J, Akca O, Lenhardt R, Sessler DI, et al. Magnesium sulphate only slightly reduces the shivering threshold in humans. *Br J Anaesth* 2005; 94(6): 756-62.

11. Powell RM, Buggy DJ. Ondansetron given before induction of anesthesia reduces shivering after general anesthesia. *Anesth Analg* 2000; 90(6): 1423-7.
12. Bock M, Bauer M, Rosler L, Sinner B, Motsch J. [Dolasetron and shivering. A prospective randomized placebo-controlled pharmacoeconomic evaluation]. *Anaesthesist* 2007; 56(1): 63-70.
13. Rohm KD, Riechmann J, Boldt J, Schuler S, Suttner SW, Piper SN. Physostigmine for the prevention of postanaesthetic shivering following general anaesthesia - a placebo-controlled comparison with nefopam. *Anaesthesia* 2005; 60(5): 433-8.
14. Sessler DI. Temperature Regulation and Monitoring. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, Editors. *Miller's anesthesia*. 7th ed. New York: Churchill Livingstone; 2010. p. 1533-57.
15. Norouzi M, Doroodian MR, Salajegheh S. Optimum dose of ketamine for prevention of postanesthetic shivering; a randomized double-blind placebo-controlled clinical trial. *Acta Anaesthesiol Belg* 2011; 62(1): 33-6.
16. Gecaj-Gashi A, Hashimi M, Sada F, Salihu S, Terziqi H. Prophylactic ketamine reduces incidence of postanaesthetic shivering. *Niger J Med* 2010; 19(3): 267-70.