Original article

A comparative study on the prophylactic effects of ketamine, dexamethasone, and pethidine in preventing postoperative shivering

Sayyed Morteza Heidari Tabaei Zavareh[1], Leyla Morovati[2], Ali Mehrabi Koushki[3]

[1] Associate Professor, Department of Anesthesiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. [2] Resident, Department of Anesthesiology, School of Medicine And Student Research Committee, Isfahan University of Medical Sciences, Isfahan, Iran. [3] Department of Epidemiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

BACKGROUND: Postanesthetic shivering is an accompanying part of general anesthesia with different unpleasant and stressful consequences for patients undergoing surgery. Therefore, its proper management is necessary for both treatment and prevention. The aim of this study was to compare the prophylactic effects of ketamine, dexamethasone, and pethidine in preventing postoperative shivering in general anesthesia. **METHODS:** In this prospective randomized double-blind clinical trial, 135 American Society of Anesthesiologists (ASA) I and II patients aged 18-70 years, scheduled for elective surgery under general anesthesia were randomized into three groups. Each group received 0.5 mg/kg intravenous (IV) pethidine, or 0.5 mg/kg IV ketamine, or 0.6 mg/kg IV dexamethasone. Central and environmental temperature and postoperative shivering were evaluated during surgery (at 0, 15, and 30 minutes) and in the recovery room (at 0-60 minutes). The values were compared between the three studied groups using analysis of variance (ANOVA) and chi-square test in $SPSS_{18}$. **RESULTS:** Each group included 45 patients. Mean values of central temperature in the recovery room were significantly different between the 3 groups ($p < 0.05$). However, the differences were not significant during surgery. Postoperative shivering was reported in 37.8%, 31.1%, and 11.1% of patients in ketamine, dexamethasone, and pethidine groups, respectively. **CONCLUSIONS:** Considering the rates and severity of shivering, variations in central temperature in the three studied groups, pethidine seems to be the most appropriate choice for preventing postoperative shivering.

KEYWORDS: Postoperative Shivering, Ketamine, Dexamethasone, Pethidine

BACKGROUND

Postoperative shivering is one of the most common problems in the early recovery phase following general anesthesia.[1] It is considered as the sixth most important problem of current clinical anesthesiology with an estimated rate of 5-65%.[2,3]

It not only makes distress in patients but also may result in different physiological changes including increased tissue oxygen consumption and carbon dioxide production which consequently increase the cardiac output and minute ventilation. These stressful physiologic conditions may cause complications in the elderly and coronary artery disease patients.[4]

Postoperative shivering was first described over 50 years ago. Though initial evidences indicated that intraoperative hypothermia and reset of thermoregulatory centers are the main causative factors, its occurrence among normothermic patients has led scientists to seek other relative factors.[5] Several studies have investigated the mechanisms responsible for postoperative shivering but the precise origin has not been clearly determined yet. A number of hypotheses have been developed in this regard and many pharmacological interventions have been investigated for management of this important postanesthetic complication. The use of some pharmacological agents such as clonidine, ketamine, doxapram, tramadol, pethidine, and other opioids has been studied in many researches.[6,7] Among the mentioned agents, pethidine is one of the most effective drugs in treatment and prevention of postanesthetic shivering. It has been suggested that pethidine could directly affect the thermoregulatory center or may act through opioid receptors. However, its underlying mechanisms have not been understood to date.[8,9]

As mentioned, different hypotheses have been recommended regarding the role of thermoregulatory and non-thermoregulatory reactions. N-methyl-D-aspartate (NMDA) receptor antagonists are among the thermoregulatory factors which might modulate thermoregulation at multiple levels. Therefore, ketamine, as a competitive NMDA receptor antagonist, could be effective for this purpose.[10] Some studies have reported its beneficial effects in this field.[11,12]

Address for correspondence: Sayyed Morteza Heidari Tabaei Zavareh, Associate Professor, Department of Anesthesiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. Email: m_heidari@med.mui.ac.ir
Received: 16.11.2011; **Revised:** 13.12.2011; **Accepted:** 23.01.2012

Regarding non-thermoregulatory factors, activation of the inflammatory responses and release of cytokines during surgery are considered as the underlying causes of postanesthetic shivering.[13] Agents with anti-inflammatory activity, such as dexamethasone, could thus reduce the occurrence of postanesthetic shivering by decreasing the gradient between core and skin temperature.[14,15]

Since postanesthetic shivering is an accompanying part of general anesthesia with different unpleasant and stressful consequences for patients undergoing surgery, it seems that its proper management is necessary for both treatment and prevention. The aim of this study was to compare the prophylactic effects of ketamine, dexamethasone, and pethidine in preventing postoperative shivering in general anesthesia.

METHODS

In this prospective, randomized, double-blind, clinical trial, 135 American Society of Anesthesiologists (ASA) I and II patients aged 18-70 years, scheduled for elective surgery under general anesthesia at Alzahra Hospital (Isfahan, Iran) in 2010, were enrolled.

Patients with a history of convulsions, hypersensitivity reaction to ketamine, dexamethasone, or pethidine, history of using tricyclic antidepressants (TCAs), monoamine oxidase (MAO) inhibitors, and β-blockers, multiple allergies, hypertension, coronary artery disease, dysautonomia, and other cardiorespiratory or neuromuscular pathology were excluded from the study. In addition, patients who were hemodynamically unstable or had severe bleeding during surgery were excluded.

The Medical Ethics Committee of Isfahan University of Medical Sciences (Isfahan, Iran) approved the study protocol and all subjects gave their written consent.

The patients were randomly allocated to receive intravenous (IV) ketamine (0.5 mg/kg), dexamethasone (0.6 mg/kg), or pethidine (0.5mg/kg), 30 minutes before the anticipated completion of surgery.

The same standard protocol was used for anesthetic management of patients in all three groups. Vital signs, oxygen saturation, electrocardiography (ECG), noninvasive blood pressure (NIBP), pulse oximetry (SpO_2), and end-tidal carbon dioxide ($EtCO_2$) were recorded before and during surgery. $EtCO_2$ during surgery was maintained at 30-35%.

Anesthesia was induced using IV fentanyl (2 μg/kg), atracurium (0.5 mg/kg), and thiopental sodium (5 mg/kg). After orotracheal intubation, anesthesia was maintained with nitrous oxide 60% in oxygen and isoflurane 1-1.5%. A 0.1-mg/kg IV dose of morphine was also administered to all patients.

Residual neuromuscular blockade was antagonized using 0.04 mg/kg neostigmine and 0.02 mg/kg atropine at the end of the surgery. During surgery, skin surface and IV fluid warming were not used. The operating room temperature was set at 22-25°C. Tympanometry was used to measure central temperature immediately after induction of anesthesia and every 15 minutes until the completion of surgery. Moreover, the temperature was measured and recorded every 5 minutes for one hour in the recovery room. Environmental temperature was also measured at the same time intervals.

After completion of surgery, the trachea was extubated when the patient had adequate respiratory efforts and properly responded to verbal commands. The type and duration of anesthesia and surgery were recorded.

In the recovery room, all patients were evaluated for postoperative shivering every 5 minutes until 15 minutes and also at 15th, 30th, 45th, and 60th minutes. The results were recorded by a trained nurse in the recovery room. The severity of shivering was evaluated by a 5-grade scale in which 0-4 corresponded no shivering, no muscle contraction but mild fasciculations in the face and neck, or peripheral vasoconstriction, visible tremor involving one muscle group, visible tremor involving more than one muscle group, gross muscular activity involving the entire body, respectively.[16] In cases with a grade 3-4 shivering for more than 4 minutes, the prophylaxis was considered ineffective and 25 mg IV pethidine was administered.

Moreover, mean heart rate, mean arterial pressure (MAP), drug side effects, level of consciousness in the recovery room, and duration of extubation were evaluated and recorded.

Side effects of the studied drugs including hallucinations, agitation, blurred vision, drowsiness, nausea, vomiting, hypotension, tachycardia, meiosis, seizure, urinary retention, numbness, dry mouth, and dizziness were recorded.

Time of discharge from the recovery room was determined using postanesthesia discharge scoring system of Aldrete and Kroulik which includes an assessment of pain, surgical bleeding, and vital signs and activity. A score of 9-10 indicated readiness for discharge.[17]

The obtained data was analyzed using SPSS18 for Windows (SPSS Inc., Chicago, IL, USA). Analysis of variance (ANOVA) and chi-square test at a significance level of $p < 0.05$ were performed to analyze the data.

RESULTS

Out of 162 eligible patients, 27 were excluded. The remaining 135 ASA I-II patients were randomly divided into 3 groups of 45. All patients were followed until the end of the study. Demographic characteristics and operative details of the 3 groups are presented in table 1.

Mean values of central temperature in the 3 studied groups during operation and in the recovery room are presented in table 2. In addition, mean values of environmental temperature in the 3 studied groups during operation and in the recovery room are presented in table 3.

Variations in central and environmental temperature (°C) in the 3 groups during operation and in the recovery room at different times are demonstrated in figures 1 and 2.

Variations in the severity of postoperative shivering in the 3 groups in the recovery room are shown in figure 3.

Overall postanesthetic shivering was seen in 36 patients including 17 (37.8%) in ketamine group, 14 (31.1%) in dexamethasone group, and 5 (11.1%) in pethidine group ($p = 0.012$). No hallucination, delirium, nausea, vomiting, hypertension, tachycardia, or other complications were seen in any of the patients.

Table 1. Demographic and operative details of patients in ketamine, dexamethasone, and pethidine groups (Values are expressed as number (%) or mean ± SD.)

	Ketamine	Dexamethasone	Pethidine	p
Demographic details				
Age (years)	45.4 ± 13.3	47.9 ± 13.6	46.5 ± 12.2	0.67
Weight (kg)	62.9 ± 8.6	67.6 ± 9.8	67.6 ± 9.4	0.02
Female	20 (44.4%)	22 (48.9%)	17 (37.8%)	Ϫ
Male	25 (55.6%)	23 (51.7%)	28 (62.2%)	0.5
ASA I	25 (55.6%)	29 (64.4%)	28 (62.2%)	0.6
ASA II	20 (44.4%)	16 (35.6%)	17 (37.8%)	Ϋ
Operative details				
Mean duration of operation (min)	57.1 ± 14	63.4 ± 16.8	64.9 ± 21	0.08
Mean extubation time (min)	11.8 ± 6.4	11.2 ± 5.6	10.9 ± 5.6	0.77
Mean duration of recovery (min)	51.6 ± 10.1	50.3 ± 12.6	47 ± 8.6	0.1

Ϋ: P-value is related to both ASA 1 and ASA2
ϪP-value is related to both sex (maleand female)

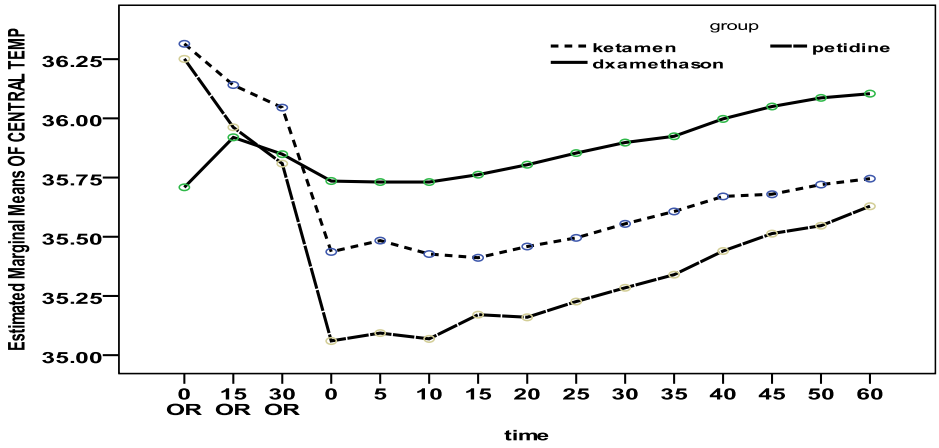

Figure 1. Variations in central temperature (°C) in the three studied groups in the operation room (OR) and recovery room at different times ($p < 0.001$)

Table 2. Central temperature in the three studied groups during operation (at 0, 15 and 30 minutes) and in the recovery room (at 0-60 minutes)

	Time (min)	Ketamine	Dexamethasone	Pethidine	p
Operation room	0	36.9 ± 0.47	36.8 ± 0.54	36.8 ± 0.42	0.37
	15	36.8 ± 0.48	36.7 ± 0.55	36.7 ± 0.44	
	30	36.7 ± 0.52	36.7 ± 0.52	36.5 ± 0.48	
Recovery room	0	36.1 ± 0.58	36.4 ± 0.5	35.8 ± 0.59	< 0.001
	5	36.1 ± 0.56	36.4 ± 0.53	35.8 ± 0.57	
	10	36.1 ± 0.54	36.4 ± 0.49	35.8 ± 0.54	
	15	36.2 ± 0.58	36.4 ± 0.5	35.8 ± 0.54	
	20	36.2 ± 0.56	36.5 ± 0.51	35.9 ± 0.6	
	25	36.2 ± 0.56	36.6 ± 0.5	36 ± 0.66	
	30	36.3 ± 0.59	36.6 ± 0.48	36 ± 0.57	
	35	36.3 ± 0.53	36.6 ± 0.49	36 ± 0.56	
	40	36.4 ± 0.55	36.7 ± 0.47	36.1 ± 0.53	
	45	36.4 ± 0.53	36.8 ± 0.47	36.2 ± 0.52	
	50	36.4 ± 0.5	36.8 ± 0.48	36.2 ± 0.5	
	60	36.5 ± 0.51	36.8 ± 0.49	36.3 ± 0.46	

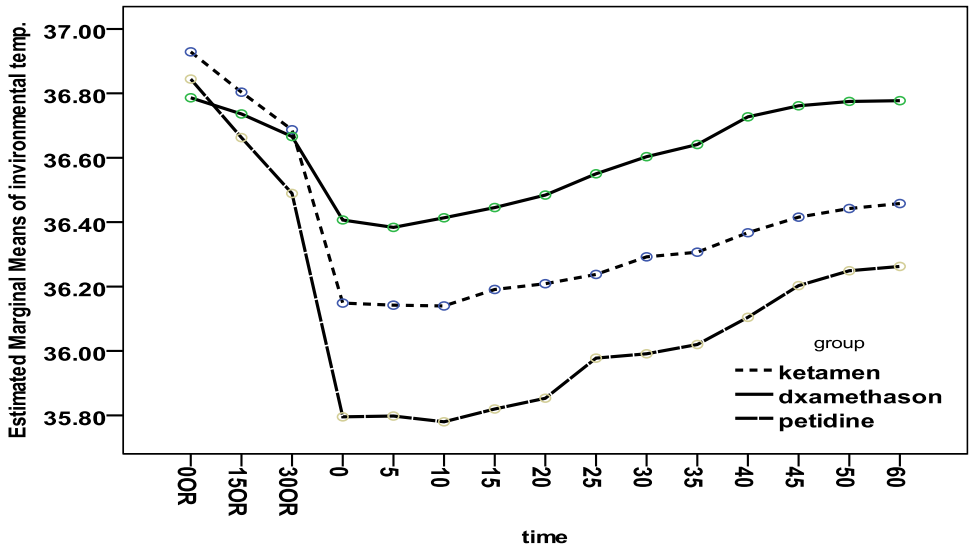

Figure 2. Variations in the environmental temperature (°C) in the three studied groups in the operation room (OR) and recovery room at different times (p < 0.001)

Table 3. Environmental temperature in the three studied groups during operation (at 0, 15 and 30 minutes) and in the recovery room (at 0-60 minutes)

	Time (min)	Ketamine	Dexamethasone	Pethidine	p
Operation room	0	36.3 ± 0.43	35.7 ± 0.9	36.3 ± 0.43	< 0.001
	15	36.1 ± 0.45	35.9 ± 0.93	36.1 ± 0.45	
	30	36.5 ± 0.49	35.8 ± 0.92	36 ± 0.49	
Recovery room	0	35.4 ± 0.52	35.7 ± 0.56	35.4 ± 0.52	< 0.001
	5	35.5 ± 0.56	35.7 ± 0.56	35.5 ± 0.56	
	10	35.4 ± 0.52	35.7 ± 0.57	35.4 ± 0.52	
	15	35.4 ± 0.55	35.8 ± 0.56	35.4 ± 0.52	
	20	35.5 ± 0.57	35.8 ± 0.54	35.4 ± 0.55	
	25	35.5 ± 0.56	35.9 ± 0.54	35.5 ± 0.57	
	30	35.6 ± 0.54	35.9 ± 0.53	35.5 ± 0.56	
	35	35.6 ± 0.5	35.9 ± 0.54	35.6 ± 0.54	
	40	35.7 ± 0.48	36.0 ± 0.53	35.7 ± 0.5	
	45	35.7 ± 0.47	36.1 ± 0.55	35.7 ± 0.47	
	50	35.7 ± 0.46	36.1 ± 0.54	35.7 ± 0.46	
	60	35.7 ± 0.45	36.1 ± 0.53	35.7 ± 0.45	

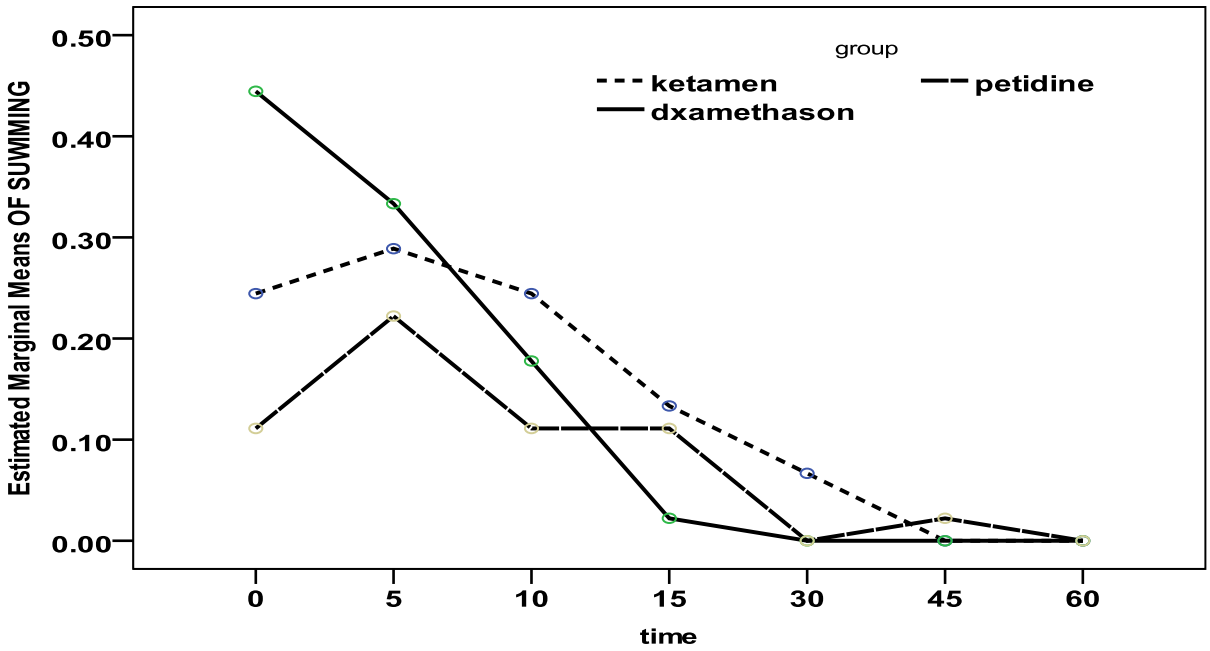

Figure 3. Variations in the severity of postoperative shivering in the three studied groups in the recovery room ($p > 0.05$)

DISCUSSION

In this study, prophylactic effects of ketamine, dexamethasone, and pethidine in preventing postoperative shivering in general anesthesia were compared. The results indicated that mean values of environmental temperature during surgery and in the recovery room were significantly different between the 3 groups. On the other hand, although mean values of central temperature in the recovery room were significantly different between the 3 groups, no significant differences were observed in values during surgery.

As mentioned, both central and environmental hypothermia during surgical procedure, especially in the recovery room, leads to postoperative shivering. Similar to previous studies,[3] we found the overall prevalence of postoperative shivering to be 26.7% (36/135). Postoperative shivering was detected in 37.8%, 31.1%, and 11.1% of patients in ketamine, dexamethasone, and pethidine groups, respectively. It was significantly different between the studied groups.

Many studies have confirmed the effectiveness of pethidine in preventing postoperative shivering. The anti-shivering mechanism of pethidine is due to its action via *k* receptor rather than μ opioid receptors.[18] However, pethidine has some adverse effects which limit its use in some cases. It may cause respiratory depression especially in patients with previous history of opioids and anesthetics administration. Other side effects are hypotension, postoperative nausea and vomiting.[19] Therefore, it seems that proper alternatives should be determined for cases with contraindications for pethidine administration.

Many studies have shown ketamine to have proper effects in preventing postoperative shivering. Some studies have also investigated different doses of the drug.[11,12] Dal et al. indicated low dose of ketamine (0.5 mg/kg) approximately 20 minutes before completion of surgery under general anesthesia, which was also administered in the current study, to be effective in preventing postoperative shivering. They concluded that ketamine can be used as an alternative prophylaxis for preventing postoperative shivering in patients with bradycardia, hypotension, respiratory depression, nausea, vomiting, and allergic reactions to pethidine.[12] In a recent study in Nigeria, the effectiveness of prophylactic low-dose of ketamine in preventing postoperative shivering has been reported.[20] Likewise, Norouzi et al. determined the optimum dose of ketamine for preventing postanesthetic shivering as 0.5 mg/kg.[21]

The role of dexamethasone as an anti-inflammatory agent in reducing the incidence of postoperative shivering, even at lower doses than that we used in the current study, has been confirmed in many studies. In two Iranian studies, Norouzi et al.[21] and Khosravi et al.[22] showed that low doses of dexamethasone (0.15 mg/kg) could properly decrease the incidence of postoperative shivering. In addition, Horn et al. indicated

that the anti-shivering effect of dexamethasone is independent of any other factors such as age, type of surgery, and duration of anesthesia.[23] In our study, the rate of postoperative shivering was lower in dexamethasone group than ketamine group.

Similar to Vaughan et al.,[24] we found a positive significant relationship between the occurrence of postoperative shivering and body temperature. In contrast, Lyons et al. suggested patients with postoperative shivering to have lower body temperature during operation and to need less active warming methods.[25]

Factors such as age, duration of surgery, temperature of the operating room, and infusion solution, which are considered as risk factors for hypothermia and shivering,[10] were similar in all groups in the present study. In addition, we tried to maintain the operation room temperature at 22-25°C and avoid using skin surface and IV fluid warming to reduce the effects of the abovementioned factors.

The limitation of our study was the short duration of surgery. The mean duration of surgical period was approximately 1 hour in all studied groups. It seems that determining the anti-shivering effects of the studied drugs in surgeries of longer duration would be more practical and conclusive because of the high risk of hypothermia in such surgeries.

In conclusion, considering the rates and severity of shivering, and variations in central and environmental temperature in our studied groups, it seems that, as reported by previous studies, pethidine is the most appropriate choice for treatment and preventing postoperative shivering. Dexamethasone would also be considered as a better alternative for pethidine than ketamine.

ACKNOWLEDGMENTS

This paper is derived from a specialty thesis in Isfahan University of Medical Sciences.Authors would like to thank all physicians and nurses of Alzahra Hospital and patients who accepted to participate in our study.

REFERENCES

1. Piper SN, Rohm KD, Suttner SW, Maleck WH, Kranke P, Boldt J. A comparison of nefopam and clonidine for the prevention of postanaesthetic shivering: a comparative, double-blind and placebo-controlled dose-ranging study. Anaesthesia 2004; 59(6): 559-64.
2. Macario A, Weinger M, Truong P, Lee M. Which clinical anesthesia outcomes are both common and important to avoid? The perspective of a panel of expert anesthesiologists. Anesth Analg 1999; 88(5): 1085-91.
3. Roy JD. Postoperative shivering. Anesthesiology Rounds 2004; 3(6): 56-60.
4. Ciofolo MJ, Clergue F, Devilliers C, Ben AM, Viars P. Changes in ventilation, oxygen uptake, and carbon dioxide output during recovery from isoflurane anesthesia. Anesthesiology 1989; 70(5): 737-41.
5. Alfonsi P. Postanaesthetic shivering. Epidemiology, pathophysiology and approaches to prevention and management. Minerva Anestesiol 2003; 69(5): 438-42.
6. Mohta M, Kumari N, Tyagi A, Sethi AK, Agarwal D, Singh M. Tramadol for prevention of postanaesthetic shivering: a randomised double-blind comparison with pethidine. Anaesthesia 2009; 64(2): 141-6.
7. Shrestha AB. Comparative study on effectiveness of doxapram and pethidine for postanaesthetic shivering. JNMA J Nepal Med Assoc 2009; 48(174): 116-20.
8. Vanderstappen I, Vandermeersch E, Vanacker B, Mattheussen M, Herijgers P, Van AH. The effect of prophylactic clonidine on postoperative shivering. A large prospective double-blind study. Anaesthesia 1996; 51(4): 351-5.
9. Roy JD, Girard M, Drolet P. Intrathecal meperidine decreases shivering during cesarean delivery under spinal anesthesia. Anesth Analg 2004; 98(1): 230-4, table.
10. De Witte J, Sessler DI. Perioperative shivering: physiology and pharmacology. Anesthesiology 2002; 96(2): 467-84.
11. Sharma DR, Thakur JR. Ketamine and shivering. Anaesthesia 1990; 45(3): 252-3.
12. 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.
13. Yared JP, Starr NJ, Torres FK, Bashour CA, Bourdakos G, Piedmonte M, et al. Effects of single dose, postinduction dexamethasone on recovery after cardiac surgery. Ann Thorac Surg 2000; 69(5): 1420-4.
14. Yared JP, Starr NJ, Hoffmann-Hogg L, Bashour CA, Insler SR, O'Connor M, et al. Dexamethasone decreases the incidence of shivering after cardiac surgery: a randomized, double-blind, placebo-controlled study. Anesth Analg 1998; 87(4): 795-9.
15. Farzi F, Sobhani A, eshtkar A. Effect of dexamethasone before induction of anesthesia on postoperative shivering . Medical Faculty Journal of Guilan University of Medical Sciences 2001; 10(39-40): 42-9.
16. Crossley AW, Mahajan RP. The intensity of postoperative shivering is unrelated to axillary temperature. Anaesthesia 1994; 49(3): 205-7.
17. Aldrete JA, Kroulik D. A postanesthetic recovery score. Anesth Analg 1970; 49(6): 924-34.
18. Wrench IJ, Cavill G, Ward JE, Crossley AW. Comparison between alfentanil, pethidine and placebo in the treatment of postanaesthetic shivering. Br J Anaesth 1997; 79(4): 541-2.
19. Terasako K, Yamamoto M. Comparison between pentazocine, pethidine and placebo in the treatment of post-anesthetic shivering. Acta Anaesthesiol Scand 2000; 44(3): 311-2.
20. 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.
21. 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.
22. Khosravi A, Moinvaziri MT, Esmaili MH, Farbood AR, Nikkhoo H, Yarmohammadi H. Treatment of postoperative shivering with dexamethasone: A prospective randomized clinical trial. IJMS 2002; 27(1): 15-7.
23. Horn EP, Standl T, Sessler DI, von KG, Buchs C, Schulte am EJ. Physostigmine prevents postanesthetic shivering as does meperidine or clonidine. Anesthesiology 1998; 88(1): 108-13.

24. Vaughan MS, Vaughan RW, Cork RC. Postoperative hypothermia in adults: relationship of age, anesthesia, and shivering to rewarming. Anesth Analg 1981; 60(10): 746-51.
25. Lyons B, Taylor A, Power C, Casey W. Postanaesthetic shivering in children. Anaesthesia 1996; 51(5): 442-5.

How to cite this article: Heidari Tabaei Zavareh SM, Morovati L, Mehrabi Koushki A. A comparative study on the prophylactic effects of ketamine, dexamethasone, and pethidine in preventing postoperative shivering. J Res Med Sci 2012; 17(Spec 2): S175-S181.

Source of Support: Nil, **Conflict of Interest:** None declared.