Prophylactic Low-Dose Ketamine to Prevent Post Anesthetic Shivering in Orthopedic Surgery: A Randomized-Controlled Study

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Objective: *Post anesthetic shivering is one of the most common anesthesia complications. We compared the efficacy of low-dose ketamine with normal saline in preventing post anesthetic shivering in orthopedic surgery.*

Material and Method: *The present study was a prospective, randomized, double-blind, controlled clinical trial involving 183 ASA I-III patients, aged 18 to 65 years whom underwent orthopedic surgery with general anesthesia. The patients were randomly allocated to receive either ketamine 0.25 mg/kg (Group K, n = 91) or normal saline (Group P, n = 92) 20 minutes before the completion of surgery. The tympanic temperature was measured before the induction of anesthesia, 30 minutes after induction, and before administration of the study drugs. An investigator, blinded to the patients' group affiliation, graded post anesthetic shivering using the Crossley and Mahajan scale. The primary outcome was to compare incidence of shivering on each group in recovery room. The secondary outcome was side effect of ketamine. Statistical analyses were performed using program R version 3.1.0. A p-value of <0.05 was considered statistically significant.*

Results: *The patient characteristics of the two groups were similar, and the number of patients with observed shivering in both groups was not statistically significantly different (Group K = 13 (14.28%) and Group P = 15 (16.30%), p = 0.42). Furthermore, in both groups, no patient suffered from hallucination, and the other complications were not statistically different.*

Conclusion: *At the recovery room, no significant efficacy difference between low-dose ketamine (0.25 mg/kg) and placebo in the prevention of post operative shivering in patients who underwent orthopedic surgery was observed. Other factors such as preload warm intravenous fluid, using active warming during surgery and control of the room temperature may help prevent shivering.*

Keywords: *Low-dose ketamine, Prevention, Post anesthetic shivering, Orthopedic surgery, Side effect*

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Both of anesthesia and surgery can cause perioperative hypothermia. General anesthesia inhibits thermoregulation in a dose-dependent manner, and induces vasoconstriction and shivering[1]. Other factors that contribute to a decrease in body temperature during surgery are ambient temperature <21°C, administration of unwarmed intravenous fluids, decreased basal metabolic rate, and heat required to humidify inhaled dry gases.

Shivering happens frequently in 5 to 60% of surgical operations. Post anesthetic shivering may predispose the patient to severe significant complications such as prolong recovery period, increase oxygen consumption, hemostatic dysfunction, especially in patients with low cardiac reserve, arterial hypoxia, which has been shown to correlate with an increased risk of myocardial ischemia, increase cardiac output, increase peripheral resistance, increase intracranial and intraocular pressure, increase carbon dioxide production, increase lactic acidosis, and interfere with electrocardiography (ECG) and oxygen saturation (SpO_2) monitoring[1]. The risks of shivering are orthopedic surgery, young age, and core hypothermia[2]. Although various drugs like meperidine, alfentanil, tramadol, magnesium sulfate, ondansetron, dolasetron, and physostigmine have been used to treat or prevent this problem, the ideal drug has not yet been found[3-6].

Ketamine is a non-competitive N-methy-D-aspartate (NMDA) receptor antagonist with a role in thermoregulation. NMDA receptors modulate noradrenergic and serotoninergic neurons in Locus coeruleus[7,8]. It is used as an antishivering agent in a low dose (0.25 mg/kg), and no significant side effects,

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e.g., mild sedation or hallucination, have been reported in previous studies[9,10]. Moreover, no difference between ketamine and pethidine in the efficacy to prevent post anesthetic shivering has been observed[11]. This finding prompted us to compare the efficacy of low-dose ketamine and placebo in the prevention of post anesthetic shivering.

Material and Method

After being approved by the Institution's Ethics Committee, we recruited patients, aged 18-65 years with the American Society of Anesthesiologists (ASA) physical status I-III, who underwent orthopedic surgery under general anesthesia. The exclusion criteria were lack of an informed consent, allergy to ketamine, body mass index (BMI) >35 kg/m², hypo- or hyperthyroidism, Parkinson's disease, severe cardiopulmonary disease, neuromuscular disease, history of convulsions, pregnancy, schizophrenia, duration of surgery <1 hour or >3 hours, body temperature before induction <35°C or >38°C, requiring blood transfusion during surgery, intake of tramadol or clonidine before surgery, received ondansetron, unable to be transferred to the recovery room, post operative used of a respirator, or intensive care unit admission.

After obtaining their written informed consents, 183 patients were divided into two groups by a computer-generated randomization sequence using sealed opaque envelopes. Group K participants received ketamine 0.25 mg/kg diluted to a volume of 2 ml by an anesthetist who was not involved in the management of patients, and group P patients received normal saline 2 ml. All patients were not administered diazepam during premedication. Before induction, non-invasive blood pressure (NIBP), SpO_2, ECG, and core temperature parameters were monitored. Preoxygenation and preload warm isotonic solution, induction was started by giving propofol 1 to 2 mg/kg, narcotic and muscle relaxant. The core temperature was measured with the Genius™ 2 Tympanic thermometer and was recorded 30 minutes after induction. Anesthesia was maintained by means of oxygen, air, and sevoflurane administration. During operation all patients were warmed by air force warmer and percentage of warming was recorded using body surface area. Before the injection of the research drug, the core temperature was measured again. We recorded the time to extubation and transfer to the recovery room for a 30-minute observation as well as the core temperature at 0, 10, 20, and 30 minutes after the completion of surgery. Shivering level was determined according to the Crossley and Mahajan scale[12] (0 = no shivering, 1 = no visible muscle activity but piloerection, peripheral vasoconstriction, or both are present (other causes excluded), 2 = muscular activity in only one muscle group, 3 = moderate muscular activity in more than one muscle group but no generalized shaking, 4 = violent muscular activity that involves the whole body). If the shivering level was greater than 3, the patient was treated with 20 mg of intravenous pethidine and active warming. In cases of nausea/vomiting, the patient received 10 mg of intravenous metoclopramide. Presence of side effects (nausea, vomiting, and hallucination) and time of first analgesia request after admission to the recovery room were also recorded.

Statistical analysis

We calculated sample size from the incidence of shivering in Songklanagarind Hospital for three consecutive years. The average incidence was 20% and the incidence of shivering in previous study was 6%[11]. Eighty statistical power and ninety-five percent confidence level were used in the present study. After calculation, sample size per group was 90.

The statistical analyses were performed using program R. Statistical significance of the variables with categorical data was determined by Fisher's exact and Chi-square tests. Student t-test was used to determine the significant difference in variables with normal distribution while statistical significance for continuous variable with non-normal distribution was evaluated by Wilcoxon Rank Sum test. The data were presented as mean (standard deviation) or median (range). A *p*-value of <0.05 was considered statistically significant.

Results

Two hundred ninety eight patients were randomized. Fifty-eight patients in group K were excluded due to their duration of surgery being >3 hours or <1 hour (n = 19), and inaccurate temperature reading was defined as the result of measurement error (n = 39), finally, 91 patients were analyzed. In group P, 53 patients were excluded as the duration of their surgeries were >3 hours or <1 hour (n = 13) and because of the temperature measurement error (n = 40), at the end, 92 patients were included in the analysis (Fig. 1).

The demographic and operative data were statistically similar between the two groups. The comparison of the number of patients between the

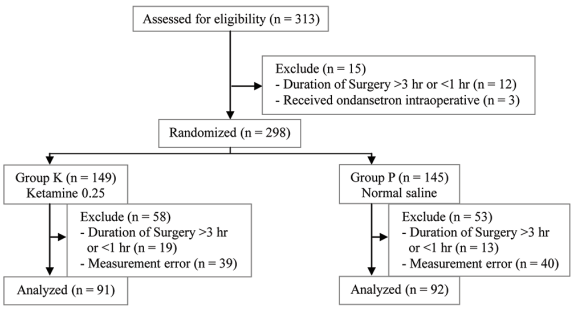

Fig. 1 CONSORT flow diagram.

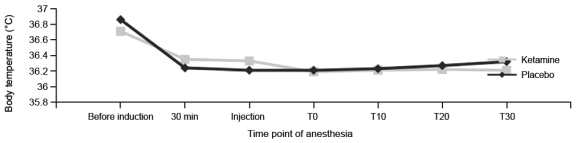

Fig. 2 The average body-temperature at the time before induction, 30 minutes after induction, at the injection of ketamine/placebo, arrival the recovery room, and 10, 20, 30 minutes after.

groups in each technique of anesthesia yielded no statistically significant difference (Table 1). No statistically significant difference in the incidence of shivering between the two groups was observed (Group K = 13 (14.28%) and Group P = 15 (16.30%), $p = 0.42$). Likewise, comparing between each technique of anesthesia, no difference in the incidence of shivering between oroendotracheal tube with a balanced technique, oroendotracheal tube with inhalation and laryngeal mask airway (LMA) with inhalation was detected ($p = 0.670$). However, this incidence for LMA with target controlled infusion (TCI) and under the mask technique could not be analyzed due to a very small sample size. When comparing the change in body temperature between the two groups, no statistically significant difference was detected (Fig. 2). The comparison between the groups in terms of shivering during the 30-minute stay in the recovery room, which was classified according to grading 0, 1, 2, 3, and 4, yielded no statistical significance as well (Table 2).

The comparison of analgesic requirement between the two groups showed that the number of patients needed analgesic drugs during the 30-minute period in the recovery room was lower in the ketamine

Table 1. Demographic and intraoperative data

Variables	Group		*p*-value
	Ketamine group (n = 91)	Placebo group (n = 92)	
Age (years), median (min, max)	40 (18, 65)	37 (18, 65)	0.22
Sex, n (%)			0.88
Male	57 (62.64)	56 (60.87)	
Female	34 (37.36)	36 (39.13)	
ASA physical status, n (%)			0.20
I	18 (19.78)	17 (18.40)	
II	60 (65.93)	69 (75.00)	
III	13 (14.29)	6 (6.52)	
Median weight (kg), (min, max)	60 (38, 94)	65 (40, 95)	0.28
Median height (cm), (min, max)	165 (138, 183)	165 (145, 192)	0.49
BMI (kg/m^2), median (min, max)	23.44 (13.96, 34.25)	23.73 (14.81, 34.06)	0.31
BSA (% of warming), mean (±SD)	22.28 (±10.62)	23.14 (±10.64)	0.59
Room temperature (°C), median (min, max)	22 (16, 26)	22 (17, 26)	0.98
Duration of anesthesia (hours), median (min, max)	2.37 (1.05, 4.08)	2.27 (1, 4)	0.66
Duration of surgery (hours), median (min, max)	1.67 (1, 3)	1.52 (1, 3)	0.62
Total fluid (ml), median (min, max)	1,000 (300, 3,200)	1,000 (400, 3,500)	0.86
Blood loss (ml), median (min, max)	50 (0, 900)	50 (0, 1,000)	0.34
Anesthetic technique, n (%)			0.96
ET with balance technique	51 (56.04)	49 (53.26)	
ET with inhalation technique	6 (6.60)	7 (7.61)	
LMA with inhalation technique	33 (36.26)	35 (38.04)	
LMA with TCI	1 (1.10)	1 (1.09)	

BMI = body mass index; BSA = body surface area; ET = endotracheal tube; LMA = laryngeal mask airway

Table 2. Comparison of shivering, classified according to grading 0/1/2/3/4, during the 30-minute stay in the recovery room between the two groups

Time (minute)	Group		*p*-value
	Ketamine group (n = 91)	Placebo group (n = 92)	
T0	80/3/1/6/1	78/4/5/3/2	0.42
T10	79/6/3/2/1	81/5/2/2/2	0.97
T20	83/2/2/2/2	84/6/2/0/0	0.20
T30	86/3/2/0/0	88/4/0/0/0	0.49

than in the placebo group; however, this difference did not reach statistical significance (ketamine = 49 (53.85%), placebo = 57 (61.96%); $p = 0.30$). Additionally, the median and IQR of time to the first request of analgesia in the ketamine group was similar to placebo group; nevertheless, once more, the difference was not statistically significant (ketamine = 10 (7.5, 15) minutes, placebo = 10 (5.8, 15) minutes; $p = 0.38$). Regarding adverse effects, no incidence of hallucinations was reported, and that of nausea/vomiting in Group K was 2.17% and 4.34% in Group P; again, there is no statistically difference between the two groups ($p = 0.68$).

Discussion

Shivering is a relatively common problem in the post anesthetic period that occurs 97 to 99% within 30 minute after recover from general anesthesia[2]. Although not a life-threatening process, it can be a source of patient discomfort and family concern. Thermoregulation is controlled by the hypothalamus and the cholinergic system. Current thermoregulatory theories do not completely explain the mechanisms of shivering following general or regional anesthesia[1].

There are multiple risk factors associated with post anesthetic shivering. In a recent observational study, Eberhart et al[2] used logistic regressions and multivariate analyses on data collected from 1,340 patients and found that there were three major risk factors: young age, endoprosthetic surgery, and core hypothermia. Age proved to be by far the most important risk factor for post anesthetic shivering because the thermoregulatory responses to cold and heat are attenuated in older patients. Regarding orthopedic surgery, the association of post anesthetic shivering can be possibly explained by the fact that such procedures are invasive, pain-intensive, and usually have a long duration. Consequently, injured tissue can release pyrogenic substances that, in turn, increase the set point of the thermoregulatory system postoperatively. Particularly, endoprosthetic surgery using bone cement is an independent risk factor for the development of post anesthetic shivering. However, the underlying biological reasons for this remain unclear. One possible explanation is that bone cement (polymethyl-methacrylate), which is often used in arthroplastic surgery, stimulates the release of cytokines such as tissue necrosis factor and interleukin-6, both of which can increase the set point of the thermoregulatory system postoperatively[2].

In the present study, the incidence of shivering in the placebo group was 16.30%, lower than that of others studies. Dal et al[8] found a shivering incidence of 60% in the placebo group, and Norouzi et al[10] reported of 73%, the dosage of ketamine was similar to our study but they did not use warming fluid and active warmer during intraoprative period. A possible explanation for this considerable difference is that in the present study, some factors that may help prevent shivering e.g., using active warming equipment during surgery and warming fluids before anesthesia induction, were used. Similarly to the present study, Vida et al[11] controlled the room temperature 23°C (±0.5), and reported a lower shivering incidence (30%) than other studies.

Regarding adverse effects, our finding of no incidence of hallucinations was similar to those of previous studies. Along the same lines was the fact that the incidence of nausea/vomiting between the ketamine (2.17%) and placebo (4.34%) groups was not statistically difference and the severity was low that no request for any treatment.

As for the analgesic effect, Vida et al[11] and Del et al[8] reported significant different times to first analgesia in the recovery room between patients receiving the ketamine dose of 0.5 mg/kg and those receiving a placebo, this finding differed from our study. We found that the patients in the ketamine group had time to first analgesia in the recovery room similarly to the placebo group. It is possible that, in our study, we used a lower dose of ketamine that is required to provide an analgesic effect (ketamine = 10 (7.5, 15) minutes, placebo = 10 (5.8, 15) minutes; $p = 0.38$).

A limitation of our study was that we did not compare other dose of ketamine.

Conclusion

No significant efficacy difference between low-dose ketamine (0.25 mg/kg) and placebo in the

prevention of postoperative shivering in the recovery room was observed.

What is already known on this topic?

Post anesthetic shivering is one of the most common anesthesia complications and may predispose the patient to severe significant complications. The risks of shivering are orthopedic surgery, young age, and core hypothermia[2]. Ketamine is used as an antishivering agent in a low dose (0.25 mg/kg), and no important side effects, e.g., mild sedation or hallucination, have been reported in previous studies[9,10]. Moreover, no difference between ketamine and pethidine in the efficacy to prevent post anesthetic shivering has been observed[11].

What this study adds?

The authors recruited only patients who underwent orthopedic surgery because of the incidence of shivering was high in this group. In this present study, the incidence of shivering in ketamine group was lower than placebo group but there was no significant efficacy difference between low-dose ketamine (0.25 mg/kg) and placebo in the prevention of postoperative shivering. So the conclusion of this study was low dose ketamine cannot prevent postoperative shivering in orthopedic surgery.

Potential conflicts of interest

None.

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การศึกษาผลของยา ketamine ขนาดต่ำในการป้องกันการสั่นหลังจากการดมยาสลบในผู้ป่วยที่ได้รับการผ่าตัดกระดูกและข้อ: การศึกษาควบคุมแบบสุ่ม

สุทธาสินี เพชรสกุล, ชณัฐี กิจศิริพันธ์, ภัณฑิลา รุจิโรจน์จินดากุล, อำพรรณ จันทโรกร, อาภรณ์ จุลบุญญาสิทธิ์, ศรัณยู ถิ่นจะนะ

วัตถุประสงค์: *การสั่นหลังจากการดมยาสลบเป็นภาวะที่เกิดขึ้นบ่อยหลังจากการผ่าตัด การศึกษานี้มีวัตถุประสงค์เพื่อเปรียบเทียบประสิทธิผลของยา ketamine กับ normal saline ในการป้องกันการสั่นหลังจากการดมยาสลบในผู้ป่วยที่มารับการผ่าตัดกระดูกและข้อในโรงพยาบาลสงขลานครินทร์ และภาวะแทรกซ้อนที่เกิดขึ้นในห้องพักฟื้น*

วัสดุและวิธีการ: *ผู้ป่วย ASA classification I-III อายุ 18-65 ปี และได้รับการดมยาสลบในการผ่าตัดกระดูกและข้อ จำนวน 183 ราย ผู้ป่วยจะถูกแบ่งเป็น 2 กลุ่ม ด้วยวิธีการสุ่มโดยใช้ computer-generated randomization ผู้ป่วยกลุ่ม K จำนวน 91 ราย จะได้รับ ketamine ขนาด 0.25 มก./กก. ส่วนผู้ป่วยกลุ่ม P จำนวน 92 ราย จะได้รับ normal saline ก่อนเสร็จการผ่าตัด 20 นาที ผู้ป่วยทุกรายจะถูกวัดอุณหภูมิที่เยื่อแก้วหูก่อนดมยาสลบ หลังดมยาสลบ 30 นาที ก่อนให้ยาวิจัยและระหว่างอยู่ในห้องพักฟื้นเป็นเวลา 30 นาที ระหว่างอยู่ในห้องพักฟื้นผู้ป่วยจะได้รับการประเมินการสั่นโดยใช้ Crossley and Mahajan scale และประเมินภาวะแทรกซ้อนที่เกิดขึ้น*

ผลการศึกษา: *อุบัติการณ์การสั่นหลังการดมยาสลบทั้งสองกลุ่มไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ กล่าวคือ กลุ่ม K = 13 (14.28%) และกลุ่ม P = 15 (16.30%), p = 0.42 และพบว่าไม่มีภาวะประสาทหลอนเกิดขึ้นกับผู้ป่วยทั้งสองกลุ่ม นอกจากนี้ยังพบว่าภาวะแทรกซ้อนที่เกิดขึ้นอื่น ๆ ในทั้งสองกลุ่มไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ*

สรุป: *ไม่มีความแตกต่างของประสิทธิผลระหว่างการใช้ ketamine 0.25 มก./กก. และกลุ่มควบคุม สำหรับการป้องกันการสั่นหลังจากการดมยาสลบในผู้ป่วยที่รับการผ่าตัดกระดูกและข้อ ปัจจัยอื่น เช่น การให้สารน้ำอุ่นทางหลอดเลือดดำ การใช้เครื่องให้ความอบอุ่นในระหว่างผ่าตัด และควบคุมคุมอุณหภูมิห้องผ่าตัด อาจช่วยป้องกันการสั่นหลังจากการดมยาสลบ*