Optimum dose of ketamine for prevention of postanesthetic shivering ; a randomized double-blind placebo-controlled clinical trial

M. NOROUZI (*), M. R. DOROODIAN (*) and S. SALAJEGHEH (**)

Abstract : Our objective was to investigate the efficacy and the optimum dosage of ketamine for post anesthetic shivering prevention.

One-hundred and twenty patients (ASA I-II) scheduled for elective orthopedic surgery were randomly allocated to receive ketamine in 3 groups ; groups A (0.125 mg/Kg), groups B (0.25 mg/Kg) and C (0.5 mg/Kg) along with those receiving 0.9% normal saline as the placebo group. Tympanic temperature was measured immediately after induction of anesthesia, 30 min after induction, before administration of the study drug and by the end of the surgery. The four groups did not differ significantly in their hemodynamic parameters and tympanic temperature. The frequency of shivering was significantly less in groups B (0.25 mg/Kg) and C (0.5 mg/Kg) than in groups A (0.125 mg/Kg) and D (placebo). In addition recovery, extubation time and hallucination was observed to be less in group B compared to group A. Prophylactic 0.25 and 0.5 mg/kg ketamine was found to be effective in preventing postanesthetic shivering with a better response observed with 0.25 mg/kg dosage.

Key words : Anesthesia ; ketamine ; shivering.

INTRODUCTION

Postanesthetic shivering is defined as an involuntary movement of one or more muscle groups which occurs during the early recovery phase following general or regional anesthesia (1). It occurs in 5-65% of patients recovering from general anesthesia (2).

The core temperature usually decreases by 0.5-1.5 °C in the first hour after induction of anesthesia ; thus, shivering may be a normal thermoregulatory phenomenon in response to core hypothermia. It could also be elicited due to cytokine release following surgery (3).

The major consequences of shivering are increase in oxygen consumption by 100-600%, increase in CO2 production and tachycardia (4, 5). Other consequences are an increase of intraocular pressure, interference with monitoring of blood pressure and ECG, increased metabolic rate, lactic acidosis and general discomfort with a sensation of feeling cold (4, 5).

A number of pharmacological interventions have been studied for the treatment and prophylaxis of shivering, including clonidine, meperidine, ketanserin, doxapram, tramadol and other opioids (6-10). Ketamine is an antagonist at N-Methyl-D-Aspartate (NMDA) receptors, which are considered to play an important role in central hypersensitivity mechanism (11). A previous randomized controlled trial suggested that it may be beneficial as a pharmacologic intervention for shivering (12). However, the ideal dose of ketamine in the treatment or prevention of shivering has not been determined as no dose-finding studies are available. The aim of this randomized, double-blind placebo-controlled trial was to find the optimum dose of ketamine to prevent postanesthetic shivering.

METHODS

This prospective randomized double-blind, placebo-controlled clinical trial and the procedures were all approved by the Ethics Committee of Kerman University of Medical Sciences. All patients read and signed the written consent form before entrance into this trial.

We studied 120 patients of both genders aged 18-65 years (ASA physical status I and II). All the patients were scheduled to undergo elective orthopedic surgery. Patients were randomly allocated to one of the four study groups each comprising 30 patients. The three first groups received ketamine in doses of 0.125, 0.25 and 0.5 mg/kg named

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groups A, B and C, respectively. Group D as the control group received 0.9% normal saline as placebo.

The exclusion criteria for our trial were: patients requiring vasoconstrictor drugs and fluid more than 2500 ml during surgery, high intracranial pressure, hypertension, Body Mass Index > 30 kg/m², psychiatric disorders, cardiac arrhythmias or heart failure (NYHA III or IV), known allergy to ketamine, fever (temperature > 37.5°C), known muscle diseases and known addiction.

Throughout the anesthesia, mean arterial pressure (MAP), heart rate (HR), and oxygen saturation were measured using a pulse oximeter. The ambient temperature in the operating room was set at 22°C. During surgery, skin surface and IV fluid warming were not used.

Tympanic temperature was measured with the Genius™ 2 tympanic thermometer, before anesthesia, immediately after induction of anesthesia, 30 min after induction and before administration of ketamine or saline. Patients with temperatures below 35°C were excluded from this study.

Anesthesia was induced using fentanyl 2 mcg/kg, midazolam 2 mg and thiopental 4 mg/kg. Atracurium 0.5 mg/kg was administered to facilitate tracheal intubation. General anesthesia was maintained with halothane 0.8% and nitrous oxide 50% in oxygen. Approximately 20 min before completion of surgery patients were randomly assigned to receive the study drug.

Residual neuromuscular blockade was reversed using neostigmine 0.04 mg/kg and atropine 0.02 mg/kg. When the patients’ respiratory effort was adequate and they responded to verbal commands, the trachea was extubated. In the recovery room, all patients were monitored, received oxygen via a facemask and were covered with a cotton blanket. An anesthetist unaware of the study drug observed the patient for occurrence of shivering and hallucination. Heart rate, non-invasive blood pressure, oxygen saturation and tympanic temperature were also measured and recorded on admission to the recovery room.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) Windows version 12.0. Demographic data, duration of surgery and anesthesia, recovery time and time spent in PACU were analyzed using the Student’s t-test. The incidence of shivering and hallucination were analyzed using Chi² test and Fisher exact test. Extubation time was compared between group by one way ANOVA and Tukey test was used to calculate the difference between each two groups. Data are shown as mean (SD) or median (range). P-value < 0.05 was considered statistically significant. Post hoc comparisons were performed with Bonferroni correction of the significance level.

RESULTS

The four groups were compared regarding age, BMI, sex, duration of surgery, extubation time and incidence of shivering (Table 1). The hemodynamic parameters and the tympanic temperatures were statistically similar in the four groups.

We found no significant relation between BMI and incidence of shivering (p-value = 0.8). Hallucination was seen in seven patients (5.8%) who received ketamine; two in group A (0.125 mg/kg), one in group B (0.25 mg/Kg) and four in group C (0.5 mg/Kg).

There was no statistical significant difference between the four study groups in hallucination rate but it occurred in 6.7% of group A (0.125 mg/kg), 3.3% of patients in group B (0.25 mg/Kg) and 13.3% of patients in group C (0.5 mg/Kg) which is approximately 4 fold of group B (0.25 mg/Kg).

Patients in group C (0.5 mg/Kg) had a significantly higher extubation time compared to the other three groups (p-value < 0.01). There was a significant difference in extubation time between four groups (one way ANOVA, p: 0.006). Post Hoc Tukey test revealed a significant difference in extubation time between group D and group C but not the other Ketamin groups (A and C) (p: 0.015). Also, extubation time was significantly different between group C (0.5 mg/Kg) and A (0.125 mg/kg) as well as group B (0.25 mg/Kg) (both, p: 0.022).

The difference of extubation time between group D (placebo) and group A (0.125 mg/kg) or group C (0.25 mg/Kg) was not significant (both, p: 0.999).

Chi square test showed that the incidence of post anesthetic shivering in group B (0.25 mg/Kg) and C (0.5 mg/Kg) was significantly less than group A (0.125 mg/kg) (p < 0.001) and controls (group D) (p: 0.018 and 0.009, respectively). There was no significant difference in shivering rate between group A (0.125 mg/kg) and control group (p: 0.1). There was no significant difference in shivering rate between groups B (0.25 mg/Kg) and C (0.5 mg/Kg), also.

Recovery time was not significantly different between the four groups (One way ANOVA).
DISCUSSION

Shivering is a relatively common problem encountered in the post anesthetic period. Although not a life-threatening process, it can be a source of patient discomfort and family concern (1, 2). Postanesthetic shivering is generally due to a thermoregulatory effect in response to core and skin hypothermia and the vasoconstriction which develops in the perioperative period (13). Thermoregulation is controlled by the hypothalamus, and the cholinergic system is likely to be among the mediators of shivering (14). Current thermoregulatory theories do not completely explain the mechanisms of shivering following general or regional anesthesia (15).

There are multiple risk factors associated with post anesthetic shivering such as: young age, duration of surgery, low postoperative temperature and anesthetic technique (1). Crossley used logistic regression analyses on data from 2595 patients and found that several variables play a role in developing post anesthetic shivering such as male sex and older ASA Physical Status (16). He also reported that older age was the most important protective factor against post anesthetic shivering (16). Current thermoregulatory theories do not completely explain the mechanisms of shivering following general or regional anesthesia (15).

Ketamine and Post Anesthetic Shivering

Table 1

Demographic characteristics, peri-operative data and incidence of postanesthetic shivering in study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ketamine (0.125 mg/kg) (n = 30) (group A)</th>
<th>Ketamine (0.25 mg/kg) (n = 30) (group B)</th>
<th>Ketamine (0.5 mg/kg) (n = 30) (group C)</th>
<th>Placebo (n = 30) (group D)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) (mean ± SD)</td>
<td>34.2 ± 14.7</td>
<td>37.8 ± 14.9</td>
<td>34.9 ± 14.4</td>
<td>39.5 ± 14.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>25/5</td>
<td>22/8</td>
<td>22/8</td>
<td>24/6</td>
<td>0.7</td>
</tr>
<tr>
<td>BMI (Kg/m²) (mean ± SD)</td>
<td>22.9 ± 2.8</td>
<td>23.6 ± 2.8</td>
<td>23.2 ± 3</td>
<td>24.9 ± 5.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Duration of surgery (mean ± SD)</td>
<td>86.2 ± 20.6</td>
<td>85.3 ± 18.2</td>
<td>85.5 ± 19.5</td>
<td>90.5 ± 18.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Extubation time (mean ± SD)</td>
<td>8.1 ± 3</td>
<td>9.1 ± 3.8</td>
<td>11.5 ± 7</td>
<td>8 ± 2.5</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Incidence of shivering ; n (%)</td>
<td>16 (53.3%)</td>
<td>13 (43.3%)</td>
<td>12 (40%)</td>
<td>22 (73.3%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hallucination n (%)</td>
<td>2 (6.7%)</td>
<td>1 (3.3%)</td>
<td>4 (13.3%)</td>
<td>0 (0.0%)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Active warming is an important intervention to prevent post anesthetic shivering (18). Various drugs have also been used to treat or prevent postoperative shivering. But a gold standard for the treatment and prevention of shivering has not been defined. Our study shows that 0.25 mg/kg ketamine, administered before completion of surgical procedures, significantly decreases the incidence of post anesthetic shivering in comparison to other doses and placebo while other advantages were also noted in this dosage. Previous studies in adults have demonstrated the efficacy of ketamine in treating and/or preventing shivering in various clinical scenarios but evidence for a specific ketamine dosage is scarce (12, 19). Ketamine, as a competitive NMDA receptor inhibitor, could prevent postoperative shivering (11). It also could control shivering by action on the hypothalamus or by the β-adrenergic effect of norepinephrine.

In a prospective trial, Dal et al reported ketamine 0.5 mg/kg to be effective in preventing postoperative shivering (12). More recently, Kose et al. prospectively studied 90 ASA I & II patients for shivering occurrence (20). This study identified much lower shivering grades for the first 4 minutes after treatment by ketamine. These studies demonstrated the role of ketamine in prevention and treatment of postoperative shivering but did not identify the optimum dosage while our study was mainly conducted to identify the optimum dosage of ketamine for prevention of postoperative shivering.

Although there was no statistical significance between 0.5 mg/kg and 0.25 mg/kg ketamine regarding the efficacy to prevent shivering, an increase in hallucinations and a delay in extubation in the 0.5 mg/kg ketamine group were noted. The 0.25 mg/kg dosage of ketamine used in our study was effective in prevention of shivering and seems to have some advantage over other ketamine dosages.
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References