

Comparison of the effect of pethidine, ketamin and ondansetron on shivering after surgery in elective laparoscopic cholecystectomy under general anesthesia

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Abstract

Background: Shivering after surgery is one of the common problems following general anesthesia and may lead to multiple complications. This study was performed to find out a suitable alternative for pethidine in prevention of post-anesthetic shivering.

Methods: In this randomized Triple-blind prospective study, 160 patients with the age of 20-50 years and ASA class I- II for elective laparoscopic cholecystectomy were classified into five equal groups. Anesthesia was induced equivalently for all. Patients were observed in terms of vital signs, side effects and shivering.

Results: The four groups were not different regarding age, gender, weight and the physical status class based on the American Society of Anesthesiologists score. Shivering after surgery was observed in 37.5% of patients in the pethidine group, 42.5% of patients in the ketamin group and 40% of patients in the ondansetron group that was significantly lower than the controls 57.5%. Changes in systolic and diastolic blood pressure, heart rate and temperature were similar in all four groups. Also the incidence of nausea and vomiting in the ondansetron group was significantly less than other groups (P value <0.05).

Discussion: Due to the significant decrease in shivering in the treatment group compared to the control group, and the stability of hemodynamic changes in all groups, with regard to a significant reduction in nausea and vomiting using ondansetron, this drug can be a good alternative to reduce shivering after general anesthesia.

Key words: General anesthesia, postoperative shivering, pethidine, ketamin, ondansetron, nausea and vomiting after surgery

Introduction

Shivering after surgery is the most common postoperative complications after surgery and is seen in between 5-65 % of patients, and includes involuntary movements of one or several groups of muscles that causes many side effects such as increased oxygen consumption, production of carbon dioxide, increase in heart rate and blood pressure and as result the intensification of ischemic heart disease, also increase in intracranial pressure, increase in intraocular pressure, increasing pain in surgical site and discomfort in the patient (1).

General anesthesia facilitates the redistribution of temperature from the central tissues to peripheral tissues. The central temperature regulation responses such as vasoconstriction threshold are inhibited by anesthesia and most anesthetic drugs cause vasodilatation of peripheral vessels (2). Recovery from general anesthesia has two phases. In the first phase temperature regulation responses have been restrained due to the residual effects of anesthesia, but in the second phase return of activities for regulation of core body temperature occurs by reducing the concentration of anesthetic drugs in the body; in this phase, if degree of body temperature is under temperature regulation threshold it leads to shivering after surgery (3).

Shivering can be the result of hypothermia during surgery and resetting center of body temperature or is due to secondary ague due to activation of the inflammatory response and releasing cytokines. There are two pharmacological methods to reduce shivering. Non-pharmacological methods include preventing hypothermia with the help of heating blankets and warm and moist oxygen inhalation. Pharmacological methods mainly effect on reducing shivering temperature threshold (5-4). Some drugs such as meperidine (pethidine) at all doses have been known to be effective for the treatment of shivering after surgery, but due to the likelihood of incidence of complications such as respiratory depression, is always considered following the use of pethidine, and to finding alternative drugs to prevent and treat shivering after surgery. But still there is some debate regarding choosing the most appropriate drug for patients after surgery (6).

The drugs that are used for the treatment of shivering after surgery are as follows: meperidine (most effective shivering treatment), clonidine, Ketanserin, tramadol, Physostigmine, nefopam, dexmedetomidine and magnesium sulfate (7).

Although the standard treatment for shivering after surgery has not been introduced it is currently most widely used among drugs in this field. Using opioids imposes enormous and unfavorable complications on patients and avoiding these complications is more important at the time immediately after anesthesia. Respiratory depression, creating nausea, vomiting, drowsiness and prolongation of time and lack of awareness of recovery time, confusion, particularly in elderly patients, disorientation, itching and constipation can prolong duration of hospitalization and impose heavy costs to the patient and the community, among these complications.

The other drugs that have been used to reduce shivering after surgery in similar studies are also not without complications (8). Clonidine, despite the decline in the incidence of shivering after surgery is significantly associated with drop in blood pressure and sleepiness. Tramadol as a non-opioid analgesic drug, in spite of inhibition of shivering after surgery can decrease sweating, vasoconstriction and shivering threshold. DOXAPRAM HCL as a brain stimulant can decrease shivering after surgery, but has significant hemodynamic effects on patients (10-9).

Ketamine is an NMDA receptor antagonist, with analgesic and anesthetic properties and in under anesthetic limit doses, relieves pain and temperature in a few steps and prevents shivering after surgery (3). Ondansetron is a well-known drug for the treatment of nausea, vomiting and a serotonin receptor antagonist that has anti shivering properties and its mechanism effect of anti-shivering is through inhibition of serotonin reuptake on an area of the anterior hypothalamic that has no opioid complications and it also has very rare complications more so than other anti-shivering drugs (11). Research has shown that the use of Ondansetron is effective in relieving shivering. Given the importance of shivering after anesthesia and with the aim of finding effective treatment with fewer side complications, this study compared the effect of analgesic therapy between the two drugs of Ondansetron and meperidine in the treatment of shivering after anesthesia.

Methodology

This triple-blind randomized clinical trial study was done on 160 patients who were under anesthesia for elective cholecystectomy in surgery in level of ASA I and II at Shahid Rajai Hospital in Qazvin in 2015. This study was approved by ethic code of 281.29 and in addition to taking written consent letter from eligible patients to enter the study they were assured of their right to opt out at any time and were assured that all information would remain confidential. Inclusion criteria to study included patients was age range between 20 and 50 years old and exclusion criteria included a history of seizures, allergies to drugs used, hypertension, cardiovascular disease, need for blood transfusion or its products, history of Parkinsons, history of chronic use of non steroidal anti-inflammatory drugs and narcotic drugs. The sample size required was calculated based on previous studies by determining sample size formula in analytical studies for each group of 40. For all patients for premedication 0.02 mg / kg midazolam and 1.5 mg / kg fentanyl was used and for induction of anesthesia 2 mg / kg protocol and 0.5 mg / kg Atracurium was injected intravenously. Propofol at a dose of 100 mcg / kg / min and alfentanil with a dose of 1 mcg / kg / min and 100% oxygen was used for maintenance of anesthesia in all patients. Normal volumes were used in all patients. Patients were randomly divided into 4 groups, by using colored cards. Three pethidine drugs at a dose of 0.4 mg / kg, 0.25 mg ketamine dose and Ondansetron with dose of 0.1 mg / kg were used for 3 intervention groups and 2 cc of normal saline was used for the control group, 15 minutes before ending surgery. It should be noted that peak of pethidine effect is 5-7 minutes and Ondansetron 10-15 minutes

and ketamine 1-4 minutes after injection of the drug. The 0.04 mg / kg neostigmine and 0.02 mg / kg atropine was used to reverse the patients in all groups. The following criteria were measured in 4 groups: blood pressure mean of systolic, diastolic, heart rate and body temperature (with the tympanic thermometer) were measured and recorded at the time of the injection before drug injection, 5 minutes after drug injection and after stabilizing in the recovery and the shivering rate and nausea and vomiting after surgery was recorded by the recovery nurse who did not know the type of each of the groups. Recovery room temperature was similar for all patients. Patients were treated alike in case of shivering in recovery.

Data were collected on the basis of check list prepared and were entered into SPSS software and analysis of qualitative values with chi-square test and Quantitative values were evaluated by ANOVA and T-Test. Repeated measure ANOVA was used to assess the changes of the parameters before and after injection of drug in the intervention and control groups. Significance level was considered equal to 5% (0.05).

Findings

In this study, 160 patients who participated were under elective cholecystectomy surgery. Samples of all four groups according to age, gender and weight were similar within each other and there was no significant difference between them.

Table 1: Comparison of mean and standard deviation of samples based on the hemodynamic and body temperature at the time before and 5 minutes after injection of the drug and after stabilizing in the four groups of study

Group	Time	Systolic blood pressure	Diastolic blood pressure	heart beat	Body temperature
Pethidine	Before injection of drug	124.2	79	75	36.6
	5 minutes after injection	125.2	78	75	36.2
	After being stable	126	75	76	36.1
Ondansetron	Before injection of drug	124.1	79	79	36
	5 minutes after injection	127.4	78	79	36.3
	After being stable	130	80	79	36.5
Ketamine	Before injection of drug	130	85	75	36.5
	5 minutes after injection	132.1	82	75	36.7
	After being stable	130	85	79	36.8
Control	Before injection of drug	124.4	79	72	36.5
	5 minutes after injection	129	77	76	36.6
	After being stable	132	80	79	36.4
		0.09	0.5	0.24	0.17

The results in Table 1 that have compared the hemodynamic changes and the mean temperature in all groups under study showed that the mean systolic and diastolic blood pressure, and heart beat rate before and after injection of drug were similar in all four groups. Mean systolic and diastolic blood pressure 5 minutes after surgery in the pethidine group did not show a significant decrease compared to the control group. We also witnessed increase in systolic and diastolic blood pressure levels in 5 minutes after injection in the Ketamine group. This difference was not significant compared to the other groups. After the being stable also hemodynamic changes were similar in all four groups. Body temperature changes in the four groups were similar in all samples, with no statistically significant difference.

Table 2: Comparison of samples' frequency based on the incidence of intensity of shivering and nausea - vomiting in four groups of research

group	Having shivering	Not having shivering	Having nausea	Not Having nausea
Pethidine	15 (37%)	25(62.5%)	16(40%)	24(60%)
Ondansetron	16 (40%)	24(60%)	1(2.5%)	39(97.5%)
Ketamine	17 (43%)	23(57.5%)	15(37.5%)	25(62.5%)
Control	23 (57.5%)	17 (42.5%)	21(52.5%)	19(47.5%)
p-value		0.02		0.01

Table 2 shows that the incidence of shivering in the three treatment groups had lower rates compared to the control group and this difference was significant (0.02), but there was no significant difference among the three groups and the frequency of shivering was similar in the three groups. The control group had the highest nausea rate in terms of frequency of nausea and vomiting and the Ondansetron group had the lowest nausea after surgery, so that in this group there was only one person with the condition. So among the three treatment groups and also among the three treatment groups compared to the control group, showed significant differences ($P < 0.05$).

Discussion

Our results showed that all three drugs had a positive effect in reducing the shivering after surgery compared with the placebo group, but there was no significant difference among the three groups. All three drugs also had a positive effect on reducing nausea after surgery compared to placebo group and in the Ondansetron group fewer patients had nausea and vomiting after surgery compared to the placebo group and this difference was statistically significant. There was no statistical difference among the groups in terms of systolic blood pressure, diastolic blood pressure and heart beat rate although these values had a higher rate in the ketamine group. Intravenous pethidine is one of the most common drugs used in the treatment of shivering after surgery but has complications such as respiratory depression, creating nausea and vomiting, sleepiness and prolongs the confusion and recovery time. These effects are of great importance, especially in elderly patients (12). Many studies have proven the better impact of pethidine in reducing shivering after surgery compared to other drugs, but research is being performed in order to find some drugs that have analgesic effect, but that do not have ongoing effects.

Ketamine is among the anesthetic drugs that can influence the temperature regulation organ to prevent shivering after surgery by blocking NMDA receptors. In recent years there has been much attention on the effects of low-dose ketamine of anesthesia limit for treatment of chronic pain and persistent neuropathies, resistant depression, control of pain after surgery and prevention of shivering after surgery (13). In the study of Pazuki, two doses of 0.3 and 0.5 mg / kg of ketamine were compared with pethidine in reducing shivering after surgery. Results showed that although the dose of 0.5 mg / kg of ketamine

has a significant effect in reducing shivering after surgery, pethidine had a more favorable effect. Also the frequency of complications was similar in both groups and only 0.5 group significant difference was observed in the incidence of nystagmus compared to the other two groups. Another study in 2008 on 90 patients with shivering of 3rd or 4th degree was performed on patients under general anesthesia. Patients were divided into 3 groups of Meperidine, with 25 mg / kg of ketamine and with a value of 0.5 and 0.75 mg / kg. In this study, unlike the present study, the rate of shivering had been controlled just for 4 minutes after entering the recovery. Although meperidine was used as a standard treatment for controlling shivering, the two amounts of ketamine were preferred compared to meperidine to control the shivering 4 minutes after administration. (15) The study is in line with Rahim's study that showed there is no difference between ketamine and pethidine in the reduction of shivering after anesthesia (16). Ondansetron is a well-known drug for the treatment of nausea-vomiting and antagonist 5 - hydroxy tryptamine. Many studies have shown that none of them have effects of opioids. In addition, no adverse effects of analgesic drugs are commonly used (extrapyramidal symptoms). Drug-sensitivity has no other known complications except for rare cases, so pharmaceutical drugs are safe to use (19-17). So in the principle study with equal number of samples in each group, the number of patients who were affected by shivering after anesthesia was lower than pethidine in the Ondansetron group, although this difference was not significantly statistical, but hemodynamic changes were similar in both groups. The number of cases of nausea in the pethidine group was more than in the other groups (20). Results of our study are also in line with this study so that Ondansetron has similarly reduced incidence of shivering compared to pethidine but significantly compared to pethidine has less decreased nausea and vomiting after

surgery. But in the study of Ranjbar the results showed that pethidine significantly reduced shivering compared with Ondansetron, but in the Ondansetron group the cases has less nausea and vomiting (21).

Conclusion

Since injection of Ondansetron and ketamine before anesthesia has reduced the shivering after surgery in comparison to pethidine, and due to the lack of hemodynamic complications in the three groups and given the significant reduction of nausea and vomiting after surgery in using Ondansetron compared to the other two groups, intravenous injection of Ondansetron can be used before anesthesia as an alternative to the administration of pethidine (as a common method of prevention and treatment of shivering after surgery) especially in patients with hemodynamic instability, and also in cases that prohibit the use of meperidine, such as high risk of respiratory depression or loss caused by creating nausea and vomiting.

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