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Comparative Efficacy Of Prophylactic Ketamine, Pethidine, And Placebo In Preventing Postoperative Shivering Following General Anaesthesia: A Randomized Double-Blind Study

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ABSTRACT

Among individuals with cardiovascular disease histories, postoperative shivering is associated with an increased risk of complications. In the study, low-dose prophylactic ketamine, pethidine, or a placebo were compared to prevent postoperative shivering. Various treatment options were compared among 90 randomly selected patients: saline, pethidine, and ketamine. The recovery period was characterized by shivering rates of 0.10, 0.10, 0.20, and 0.30. Neither dose of pethidine nor ketamine produced shivering at T0 or T10. However, neither treatment differed significantly at T30. Despite pethidine's effectiveness, ketamine failed to demonstrate any benefit despite its effectiveness. We found that both drugs were highly tolerated, and no severe adverse reactions occurred. Developing a simplified dosing regimen will require future research.

Keywords: Postoperative shivering, pethidine, ketamine, prophylaxis, general anaesthesia.

INTRODUCTION

Shivering occurs after general anaesthesia in 5-65% of patients that have undergone a general anaesthetic procedure and after epidural anaesthesia in 30% of volunteers. Shivering postoperatively may be caused by a variety of factors, including periodic thermoregulation caused by hypothermia or release of cytokines following surgery. During the first hour after induction of anesthesia, the core body temperature can decrease by 0.5 to 1.5 degrees Celsius【1, 2】. Autonomic thermoregulation is generally impaired during general anesthesia. Normal-temperature patients can also shiver as a result of anxiety following anesthesia or after surgery. When patients have coronary artery disease or suffer from any other health condition, shivering during surgery can be both painful and exhausting. As a result, oxygen consumption increases (by 100-600%), cardiac output increases, carbon dioxide is delivered, and catecholamine levels increase, but mixed venous oxygen saturation goes down significantly. As well as increased intracranial and intraocular pressure, the disorder interferes with monitoring ECGs and blood pressures, as well as increased metabolic rate and lactic acidosis. Postoperative shivering has been treated or prevented with a variety of drugs, including pethidine, ketanserin, sufentanil, alfentanil, tramadol, physostigmine, urapidil, nefopam, doxapram, and nalbuphine. Pethidine is considered to be the most effective of these drugs. According to current theory, pethidine works either directly or indirectly on the thermoregulatory center. In addition, NMDA receptor antagonists may influence thermoregulation as well. Ketamine, a competitive antagonist of NMDA receptors, has been shown to block the shivering that occurs after surgery. Ketamine, however, has yet to be investigated in terms of its use preoperatively to prevent shivering. This study aimed to evaluate whether prophylactic ketamine prevents post-operative shivering more effectively than pethidine or a placebo.

METHODS

All participants signed informed consent and participated in a prospective, randomized, and blinded study. Ninety men and women between 18 and 65 years of age were recruited for this study. Anesthesia lasting 60 to 180 minutes was administered to six subjects, all classified as ASA I or II. We excluded patients who received blood transfusions or had urological endoscopic surgery. Patients with a BMI greater than 30 kg/m2, allergies, hypertension, coronary artery disease, or other conditions related to cardiorespiratory or neuromuscular systems were eligible. In an envelope-randomized study, participants received saline, 20 mg pethidine, or 0.5 mg/kg ketamine intravenously 20 minutes before surgery. Patients were not directly involved in the preparation and administration of study medications. Anesthetists handled both functions. There was a standardization of anesthesia protocols for all participants. Patient information about

the VAS was given prior to surgery. Monitoring of heart rate, noninvasive blood pressure, and oxygen saturation took place throughout the procedure. We measured tympanic temperature immediately after induction, 30 minutes later, and before administering ketamine, pethidine, or saline to the subjects.
In addition, temperatures below 35 degrees Celsius were not considered, and those between 35 and 36 degrees Celsius had to be heated. When intubating the patient, propofol (2 mg/kg), fentanyl (1 g/kg) and vecuronium (0.1 mg/kg) were administered intravenously. Anesthesia was provided by nitrous oxide and 60 percent oxygen, along with 2-4 percent sevoflurane. Additional doses of vecuronium (0.03-0.05mm/kg) were given ad hoc as needed. A random selection of patients was conducted twenty minutes before surgery to receive the study drug. By combining 300 mg/kg of neostigmine with 100 mg/kg of atropine, the effects of neuromuscular blockade were reversed with 0.25 grams of neostigmine and 0.01 grams of atropine. Patient intubation was performed when the patient's respiratory effort was good, and he obeyed verbal instructions. Several studies have examined the type and duration of surgery and anesthesia. In addition to oxygen masks that provided oxygen, cotton blankets kept the patients warm after they had recovered. A nurse anesthetized the patients and observed them for shivering, pain, nausea, and vomiting during anesthesia. The data collected when the patient arrived in recovery as well as at T0, T10, T20, and T30 included heart rate, non-invasive blood pressure, oxygen saturation, and tympanic temperature. An assessment of shivering was conducted with a four-point scale (Table 1). The pain was measured by a 0-10 cm visual analogue scale. There was a difference of 10 between no pain and the most severe pain. During recovery, pain levels were recorded at T0 (within an hour of arrival) and T1 (as soon as one hour had passed). Furthermore, hallucinations, nausea, vomiting, hypotension, tachycardia, and hypertension were monitored in the study. Several times a day, metoclopramide (10 mg i.v.) was administered to treat nausea and vomiting. On a VAS over 3, methamizole infusions were administered for 30 minutes along with 20 mg of phenylephrine. The intravenous administration of pethidine was used in cases of shivering grade 2 or more. A study examined how much and when to use the drug within the first two hours of surgery [11,12].

STATISTICAL ANALYSIS

An analysis of variance was performed on the mean differences between the groups for age, weight, and height. This variable's means for each group were compared by analysis of variance (ANOVA). Comparing pain scores among groups was done using the Kruskal-Wallis test. A chi-square test was used to analyze the differences in gender, ASA classification, shivering, analgesic requirement, and nausea or vomiting. In order to be statistically significant, a significance level of P 0.05 must be met. Bonferroni corrections were used when comparing post-hoc results. The chi-square test can be powered at 93% with 30 individuals per group, a significance level of 0.01 and an expected proportion of 0.66.

RESULTS

Table 1: Despite the same treatment, the patient groups differed. A number can be expressed as a mean, a range or a standard deviation.

Group	Group S (n=30)	Group P (n=30)	Group K (n=30)
Age (yr)	42 (19–64)	44 (19–64)	46 (20–65)
Female/male	22/8	23/7	22/8
Weight (kg)	66 (7)	70 (9)	64 (8)
Height (cm)	165 (7)	163 (9)	161 (7)
ASA I/II	24/6	25/5	24/6

Table 2: There were differences in the levels of shivering among the three treatment groups. There will be a calculation for the time at T0 in the recovery room, followed by the time at T10, followed by the time at T20 and finally by the time at T30 in the recovery room. A radical X is derived by dividing Group S by Group K by Group P. A radical X is derived by dividing Group S by Group Q.

Grade 0/1/2/3	Group S	Group P	Group K	P-value
T0	17/5/4/4	30/0/0/0*	30/0/0/0{	<0.001
T10	14/6/5/5	30/0/0/0*	29/1/0/0{	<0.001
T20	21/9/0/0	30/0/0/0*	27/2/1/0{	<0.008
T30	26/3/1/0	30/0/0/0	27/2/1/0	0.088

In this study, various pharmacological techniques were evaluated to prevent postoperative shivering. Various types of ketamine were administered to three groups: Group S (saline), Group P (pethidine), and Group K (ketamine). As shown

in Table 1, all groups had similar ASA classifications, weights, heights, and ages. Among all groups of patients, a majority of them were female, with a median age between 19 and 65 years. A total of four time intervals were used to measure postoperative shivering: on arrival in the recovery room, after 5 minutes, 10 minutes, 20 minutes, and 30 minutes. Pethidine and ketamine significantly reduced shivering rates in Group P and Group K compared with Saline (Group S). Shivering was not reported by any patients in Group P or Group K at T0, whereas there were more patients in Group S who exhibited shivering (grades 5 or 4). A similar pattern was observed at T10, when Groups P and K did not shiver at all, whereas Group S experienced moderate shivering (14/6/5/5). Even though shivering levels significantly changed between T20 and T30, Group S continued to demonstrate a higher incidence of shivering than Group S. However, Group P and Group K did not differ significantly in preventing shivering at T30 (P = 0.088). Ketamine and pethidine are effective in treating postoperative shivering because they reduce shivering after surgery. It may also help heal wounds after surgery when used with ketaminess.

DISCUSSION

Shivering following surgery has been treated with several medications, but none are definitively effective. Several studies have demonstrated the effectiveness of pethidine. In contrast, none of the patients without prophylactic treatment shivered. According to one experiment, pethidine may primarily work on mu receptors rather than kappa receptors when combined with naloxone. As a result of naloxone's inhibitory effect on pethidine's antishivering action, both mu and kappa receptors were affected, not just at low doses. In addition, pethidine can cause respiratory depression when combined with other opioids or anesthetics. Pethidine also causes nausea and vomiting. Shivering after surgery can also be inhibited by ketamine, an NMDA antagonist. A variety of mechanisms are involved in the influence of NMDA receptor antagonists on thermoregulation. The preoptic and anterior hypothalamus have been shown to be activated by NMDA in animal models. The locus coeruleus is also stimulated by NMDA receptors, which stimulate noradrenergic and serotonergic neurons. Serotonin, in turn, enhances NMDA receptor activity. Additionally, NMDA receptors are known to regulate nociceptive transmission in the dorsal horn. It acts as a local anesthetic in addition to inhibiting monoamine uptake, inhibiting descending inhibitory monoaminergic pathways, and blocking muscarinic receptors. The action of norepinephrine on beta-adrenergic receptors modulates shivering by modulating non-shivering thermogenesis. There were three patients who experienced grade 2 shivering despite receiving ketamine prophylaxis in our study. Intravenous pethidine was then given to these patients. There may be a difference in the mechanism of action between pethidine and ketamine. In our study, we used 1.0 mg/kg of ketamine, which has been reported to be effective for treating postoperative shivering in previous studies. An investigation in the British Journal of Anaesthesia found that ketamine had analgesic and sedative effects on 30 patients undergoing spinal and epidural anesthesia after halothane. Hallucinations were experienced by two patients, while delirium was experienced by four others. It is noteworthy that no side effects were observed when ketamine was administered 20 minutes prior to anesthesia induction. It is important to consider the possibility of hallucinations when taking ketamine, despite its effectiveness.
This study found that ketamine and pethidine had the same effect of preventing postoperative shivering. No other study has been found that has compared postoperative shivering with the use of prophylactic ketamineA study conducted by the same team found that 60% of placebo participants showed shivering after surgery, which is in line with studies conducted by other researchers. In addition to spinal reflexes, pain, sympathetic dysfunction, pyrogenic mediator release during surgery, volatile anesthetics, opioid withdrawal, blood loss, and the length of the surgery, as well as hypothermia's thermoregulatory effects, shivering can be caused by a variety of factors. This study, however, did not find any association between axillary temperature and shivering. The surface of the skin can be warmed, radiant heat can be applied, or pharmaceutical intervention can be used to relieve shivering.

Our study found that tympanic temperatures did not differ significantly between groups, and all patients maintained a temperature above 36°C without active warming. First analgesic doses were administered to placebo patients less than 25 minutes after the first analgesic dose in the ketamine and pethidine groups. A painkiller (methamizole or pethidine) was administered to all three groups within two hours after surgery. The short acting properties of pethidine and ketamine make them likely to have rapid effects at low doses. Researchers have studied the effects of pethidine and methamizole on reducing postanesthetic shivering, but little is known about their effectiveness. It is possible that methamizole would have enhanced pethidine or ketamine's antishivering effect within 30 minutes after surgery due to its analgesic effects. Shivering, however, might occur if pethidine were administered immediately after surgery instead of preventing it. Whenever pethidine is combined with other opioids or anesthesias, it may cause respiratory depression. There is also a tendency for nausea and vomiting to occur. Although the study lacked the power to clearly demonstrate a difference between the two drugs, ketamine has the potential to show superiority in respiratory depression, nausea, and vomiting. Ketamine may be useful as a treatment for postoperative shivering, especially to prevent shivering in patients with bradycardia, hypotension, respiratory depression, nausea, vomiting, or pethidine-induced allergies. In future studies, it may be possible to establish this by optimizing ketamine doses.

CONCLUSION

Neither pethidine nor ketamine were significantly different in terms of effectiveness in preventing postoperative shivering. Additionally, pethidine and ketamine significantly reduced occurrences of shivering compared to placebo. Neither group showed any signs of shivering in the beginning (T0) nor at the end of the study (T10). Even though it inhibited shivering similar to ketamine and pethidine, it may have been beneficial to patients experiencing respiratory depression, nausea, or vomiting. Despite the risks associated with pethidine, it is still a commonly used treatment method, especially when used alongside other opioids and anaesthetics. It is important to note that although ketamine does not cause hallucinations, side effects could still occur. Aside from further determining the optimal dosage regimen of ketamine, more studies are needed to evaluate ketamine's potential for treating postoperative shivering instead of pethidines.

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