



A Comparative Study on Different Doses of Pethidine and Ketamine for Prevention of Shivering During and After Spinal Anesthesia at Cesarean Section

Hasan Zabetian^{1,3}, Navid Kalani^{2*}, Mohammad Sadegh Sanei^{1,3}, Mansour Deylami⁴, Hossein Kargar Jahromi⁵ and Farzad Poorgholami¹

¹Research center for Social Determinants of Health, Jahrom University of Medical Sciences, Jahrom, Iran

²Medical Ethic Research Center, Jahrom University of Medical Sciences, Jahrom, Iran

³Department of Anaesthesiology, Jahrom University of Medical Sciences, Jahrom, Iran

⁴Department of Anaesthesiology, Golestan University of Medical Sciences, Golestan, Iran

⁵Research center for non-Communicable Diseases, Jahrom University of Medical Sciences, Jahrom, Iran

Correspondence Email: navidkalani@ymail.com

ABSTRACT

Postoperative shivering is a common complication during anesthesia, which is usually accompanied with other problems such as increased oxygen intake, increased intracranial pressure and several other complications. This study attempted to compare different doses of pethidine and ketamine for prevention of shivering during and after spinal anesthesia at cesarean section. This was a double-blind randomized clinical trial comprising a population of 45 pregnant women in three 15-subject groups receiving 0.3 and 0.15 mg of ketamine per kg body weight as well as 25 mg of pethidine. Admitted to Motahari Hospital in Jahrom (Iran), the subjects went through selective cesarean section under spinal anesthesia. Data were analyzed through SPSS 16, t-test, Chi-square and Kruskal–Wallis. The P-value was considered significant at lower than 0.05. As for ketamine 0.15, on patient (6.7%) experienced mild shivering at 5, 10, 15 and 30 minutes. The intensity of shivering in recovery between ketamine 0.3, ketamine 0.15 and pethidine 25 mg was not significant at 5, 10, 15, 30 and 45 minutes (p -value > 0.05). Although a dose of 0.15 and 0.3 mg per kg led to shivering control, pethidine was still a better choice for shivering control.

Keywords: pethidine, ketamine, shivering.

INTRODUCTION

Shivering is defined as involuntary movement of one or more muscles appearing in the first stage of local or general anesthesia [1 and 2]. Nowadays, postoperative shivering has become a common phenomenon with the increasing number of surgeries [3]. In fact, it occurs among 50-65% of patients in the awakening state of general anesthesia and more than 33% of patients under local anesthesia [4 and 5]. Shivering usually initiates in the recovery room and following the return of muscle tone, which feels very unpleasant for the patient [6, 7]. The exact etiology of postoperative shivering is still not fully understood. There are a number of risk factors such as reduction in core body temperature, inhibition of spinal reflexes, postoperative pain, and reduced activity of the sympathetic system, discharge of fever-causing substances, adrenal suppression and metabolic alkalosis [7, 8]. In addition to causing stress in patients, shivering leads to more prominent complications such as increase in oxygen intake by 60 percent, increase in cardiac output, higher heart rate, lower blood oxygen, increased intracranial pressure, post-surgery pain

and impaired cardiac monitoring and pulse oximetry [5 and 7]. Postoperative shivering is usually caused by unintended hypothermia during surgery [9, 10]. Spinal anesthesia inhibits all the heat messages in the blocked area, mostly the cold messages, thus curtailing the verge of shivering in vasoconstriction mechanism. In addition, spinal anesthesia create vasoreactivity dilatation due to sympathetic block, thus leading to body temperature drop and making the patient prone to hypothermia and shivering. The condition increases oxygen intake, higher carbon dioxide production, hypoxia, increased blood pressure, increased intracranial pressure, increased intraocular pressure, pain intensified in the operative site and opening of wound sutures [13-11]. Several medical and non-medical strategies have been suggested for treatment and prevention of shivering [8]. The non-medical measures include keeping the operating room warm during surgery [8]. Given that the entire surface of the skin is involved by 20 percent in the control of body temperature, this procedure is not sufficient to control the central hypothermia recovery. Hence, it is essential to use medical actions for treatment [6]. Pethidine is an opioid hair-receptor agonist, which significantly inhibits the reuptake of five hydroxy triptans. The analgesic effect of Pethidine initiates by attaching to of Alpha-2 adrenergic receptor in locus coeruleus, thus creating agonist effects [14]. In a study by Wikers *et al* [2001], the effects of tramadol and pethidine were compared in postoperative shivering control in Taiwan, indicating that pethidine was preferred over tramadol for controlling the postoperative shivering [15]. In recent years, much attention has been paid to the effects of low-dose ketamine anesthesia for treating chronic resistant pain, neuropathy, resistant depression, post-surgery pain control and prevention of postoperative shivering [16]. Ketamine is an anesthesia drug and also an antagonist, characterized by pain-relieving effect at sub-anesthetic doses. Moreover, it can progressively regulate temperature and prevent shivering [17]. In a study by Zahra *et al.* [2008], the advantages of intramuscular ketamine was examined in prevention of postoperative shivering among children [18]. In another study by Kuseh *et al.* [2008], the effectiveness of ketamine was examined in the treatment of postoperative shivering [19]. Yet in another study by Paier *et al* [2008], the results showed that ketamine infusion immediately after cardiac surgery can reduce postoperative nausea and vomiting [20]. Ketamine is an anesthetic and analgesic drug with sympathetic effects. Due to its impact on higher blood pressure and hemodynamic stability, it can be useful for spinal anesthesia. Moreover, ketamine can control shivering by thermogenesis through hypothalamus or beta-adrenergic effect of norepinephrine. In addition, ketamine has analgesic effect due to antagonist receptor on NMDA [N-methyl-D-aspartate], which is effective in controlling non thermoregulatory control [21]. Hence, this study intended to evaluate low-dose ketamine and pethidine in preventing as much a possible the shivering during and after spinal anesthesia in cesarean section.

MATERIALS AND METHODS

This was a double-blind randomized clinical trial with a population of 45 pregnant women with class 1 and 2 anesthesia by American Society of Anesthesia (ASA) ranging from 18 to 35 years old. Admitted to Motahari Hospital in Jahrom (Iran), the subjects went through selective cesarean section under spinal anesthesia. After receiving permission from the Ethics Council of the University and obtaining the informed consent from patients to participate in the scheme, the subjects were divided randomly into three groups of 15. Patients in group A received ketamine 0.3 mg per kg of body weight intravenously, while group B received ketamine 0.15 mg per kg of body weight intravenously and group C received 25 mg of intravenous pethidine. The inclusion criteria were no history of hallucination and delirium, insensitivity to medication, no history of heart problems, no history of high blood pressure, high eye pressure and heart palpitations. Furthermore, the patients were excluded in case of any unforeseen accident taking place during caesarean section, requiring injection of other drugs, hemodynamically compromising the patient life, or if the spinal anesthesia turned into general phase. All the patients received sufficient preoperative serum. During the surgery, oxygen was prescribed at 5 liter per minute through a face mask. When entering the operating room, Blood Pressure, respiratory rate and Heart Rate (HR) of patients were registered. All the patients went through spinal anesthesia with a specific procedure and 75 mg of 5% lidocaine. Spinal anesthesia took place under sterile conditions and spinal needle Quincke 25 G into L3-L4 or L4-L5. The patient was immediately placed in supine position while keeping the anesthesia level by pinprick test at T4-T6. Patients did not receive any pre-medication, the temperature of surgery room was between 21 and 22 °C and the intravenous fluids received by the patient was the same room temperature as the room. During the surgery, standard monitoring of blood pressure, arterial oxygen saturation, heart rate and electrocardiogram was performed. The tympanic temperature of patients before spinal anesthesia at 5, 10, 15, 30 and 45 minutes was measured by tympanic thermometer. From the beginning to the end of the operation, the patient's vital signs were recorded at 5, 10, 15, 30 and 45 minutes. The side effects of shivering such as nausea, vomiting, low blood pressure (hypotension) and a drop in heart rate (bradycardia) were recorded in case they occurred. The patients were excluded if there was more than 22% drop than the base rate in mean arterial pressure as well as nausea and vomiting. Immediately after delivery, the patients

were randomly given a dose of ketamine 0.15 mg Per Kg together with midazolam at a dose of 0.03 mg/kg or ketamine at a dose of 0.3 mg/kg together with midazolam at a dose of 0.03 mg/kg or pethidine at a dose of 25 mg together with midazolam at a dose of 0.03 mg/kg. At the end of surgery and in the recovery room, it was determined whether or not there was shivering within 45 minutes based on several criteria including without shivering=0, minor fasciculation in face and neck, ECG abnormalities in absence of voluntary arm activity (1=mild shivering), visible tremor of more than one muscle group=2 (moderate shivering), severe muscle activity throughout the body=3(severe shivering), which have been graded by Matthews et al. In addition to examining whether there was shivering in recovery, the blood pressure, heart rate and oxygen saturation were monitored before surgery and in the recovery room (at times 5, 10, 15,30 and 45 minutes). Moreover, the side effects ketamine such as hallucination and involuntary eye movements and unusual drowsiness, vomiting, excessive sleepiness were recorded. The data were analyzed through SPSS 16. The dependent variables were examined in terms of normal distribution through t-test and abnormal distribution through the Mann-Whitney nonparametric equivalent. Moreover, the nominal qualitative variables were evaluated through Chi-square test, while the ordinal qualitative variables were evaluated through the Mann-Whitney test. The P-value was considered significant at lower than 0.05. In all phases of the research, the Declaration of Helsinki and principles advised by the Ethics Committee at Jahrom University of Medical Sciences were observed.

RESULTS

The patients were divided into three 15-subject groups. In this respect, Group A received ketamine 0.3 Mg /g, Group B received ketamine 0.15 mg /kg and group C received 25 mg of pethidine. The average duration of action in ketamine 0.15 mg group, ketamine 0.3 and pethidine was 43±16, 40.67±7 and 42±16 minutes, respectively. In this regard, there was no significant difference (Table 1).

Table 1: Comparing the average operation time between ketamine 0.3 and ketamine 0.15 mg and pethidine at 5, 10, 15, 30, 45 minutes through the Kruskal-Wallis test

dose	N	Mean±SD	T	p-value
ketamin 0.15	15	43±16	0.512	0.612
ketamin 0.3	15	40.67±7		
petedin	15	42±16	0.319	0.853

Compare Chi-square test results show that the intensity of shivering during operation between ketamine 0.3 mg 0.15 mg ketamine and 25 mg pethidine was not significant at 5, 10, 15, 30, 45 minutes (p-value> 0.05). The majority of patients experienced no shivering in terms of intensity. As for ketamine 0.15, 6.7% of patients experienced extremely severe shivering at 15 minutes, 6.7% of patients with moderate shivering, while 6.7% experienced extremely severe shivering at 30 minutes. As for ketamine 0.3, 6.7% of patients experienced mild shivering at 15 minutes, while 13.3% experienced mild shivering at 30 minutes. Moreover, intensity of shivering in the pethidine group was zero. (Table 2).

Table 2: Comparing the intensity of shivering during operation between ketamine 0.3 mg and ketamine 0.15 mg and pethidine at 5, 10, 15, 30, 45 minutes through the chi-square test

Intensity of shivering	dose									Pearson Chi-Square	P-value
	ketamin 0.15				ketamin 0.3				petedin		
	Do not have	Mild	Average	Severe	Do not have	Mild	Average	Severe	Do not have		
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)		
5 min	15(100)	0(0)	0(0)	0(0)	15(100)	0(0)	0(0)	0(0)	15(100)	-	-
10 min	14(93.3)	1(6.7)	0(0)	0(0)	15(100)	0(0)	0(0)	0(0)	15(100)	2.045	0.360
15 min	13(86.7)	0(0.0)	1(6.7)	1(6.7)	14(93.3)	1(6.7)	0(0)	0(0)	15(100)	6.143	0.407
30 min	14(93.3)	0(0.0)	0(0)	1(6.7)	13(86.7)	2(13.3)	0(0)	0(0)	14(100)	5.938	0.204
45 min	9(100.0)	0(0.0)	0(0)	0(0)	15(100)	0(0)	0(0)	0(0)	6(100)	-	-

Comparing the results of Chi-square test indicated that the intensity of shivering in recovery between ketamine 0.3 mg and ketamine 0.15 mg and pethidine 25 mg was not significant at 5, 10, 15, 30, 45 minutes (p-value> 0.05, Table 3). As for ketamine 0.15, 6.7% of patients experienced extremely severe shivering at 5 , 10 , 15 , 30 minutes.

In ketamine 0.3 mg 5 minutes, 6.7% of patients had mild shivering, 6.7% of patients had moderate shivering at 10 minutes, 6.7% of patients had severe shivering at 15 minutes, 6.7% of patients severe in 30 minutes, and 6.7% had zero shivering at 45 minutes. Moreover, intensity of shivering in the pethidine group was zero.

Table 3: Comparing the intensity of shivering between ketamine 0.3 mg and ketamine 0.15 mg and pethidine in recovery at 5, 10, 15, 30, 45 minutes through the chi-square test

Intensity of shivering	dose									Pearson Chi-Square	P-value
	0.15				0.3				Pethidine		
	Do not have	Mild	Average	Severe	Do not have	Mild	Average	Severe	Do not have		
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)		
5 min	14(93.3)	1(6.7)	0(0)	0(0)	14(93.3)	1(6.7)	0(0)	0(0)	15(100)	1.047	0.593
10 min	14(93.3)	1(6.7)	0(0)	0(0)	14(93.3)	0(0)	1(6.7)	0(0)	15(100)	4.047	0.400
15 min	14(93.3)	1(6.7)	0(0)	0(0)	14(93.3)	0(0)	0(0)	1(6.7)	15(100)	4.047	0.400
30 min	14(93.3)	1(6.7)	0(0)	0(0)	14(93.3)	0(0)	1(6.7)	0(0)	5(100)	2.687	0.612
45 min	9(100.0)	0(0.0)	0(0)	0(0)	10(100)	0(0)	0(0)	0(0)	3(100)	-	-

Comparing the results of Chi-square test indicated that hallucination and nausea in recovery between ketamine 0.3 mg and ketamine 0.15 mg was not significant at 5, 10, 15, 30, 45 minutes(p-value> 0.05).

DISCUSSION

Due to potential severe damage caused by sympathetic stimulation, increased oxygen intake and carbon dioxide production in patients, prevention and treatment of postoperative shivering is an integral part of patient care after surgery [26]. Hence, this study intended to evaluate low-dose ketamine and pethidine in preventing as much a possible the shivering during and after spinal anesthesia in cesarean section. Ketamine is an anesthetic and analgesic drug with sympathetic effects. Due to its impact on higher blood pressure and hemodynamic stability, it can be useful for spinal anesthesia. Moreover, ketamine can control shivering by thermogenesis through hypothalamus or beta-adrenergic effect of norepinephrine [27]. The main problem with the use of pethidine lies in its exacerbated effect on the central nervous system, respiratory depression and severity of nausea and vomiting especially in patients undergoing anesthesia and surgery previously receiving sedative drugs [28]. In some studies, ketamine at a dose of 0.75 mg/kg led to lower shivering as compared to pethidine, but there side effects such as Nystagmus and subsequently lightheadedness [22 and 19]. In a study conducted in 2008, the effect of prophylactic ketamine was examined on postoperative shivering, where the patients received 20 minutes before the end of surgery 0.5 mg/kg of ketamine. In this study, ketamine was used as prophylaxis and all patients were under general anesthesia. There were a total of 30 patients in the ketamine group and 10 patients in the pethidine group. The shivering intensity was measured at 10 and 20 minutes after surgery. This study was consistent with the current one, because there was no significant difference between pethidine and ketamine in terms of controlling the intensity of shivering [28, 29 and 21]. The results of a study in India examined doses of 0.5 mg. and 0.75 mg and pethidine 0.25 mg, finding out that both doses of ketamine were preferable over pethidine in shivering control. The results were inconsistent with those of the current one [21]. The patients were compared in term of rise and fall in blood pressure, even though the difference was not statistically significant. In that study and the one conducted by Kuseh, there was no difference in terms of the complications [19].

CONCLUSION

Accordingly, 0.3 mg per kg of ketamine is more effective than 0.15 mg per kg of ketamine for controlling postoperative shivering. According to our findings, however, pethidine is still the more ideal standard medication for prevention of postoperative shivering. Due to its availability and analgesic properties, ketamine can be applied in cases where there are restrictions in using pethidine.

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