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Comparing the Effectiveness of Antishivering Action of Meperidine Alfentanil, Sufentanil, Fentanyl and Tramadol After General Anesthesia.

Sajedi P*, Nazemroaya B**.

* Associate professor and ** Resident, Department of Anesthesia and Critical Care, Isfahan University of Medical Sciences, Isfahan, Iran.

Correspondence: Dr. Parvin Sajedi, P.O.Box 896 AL-Zahra Medical Center, Isfahan, Iran, Tel: +98(311)776-9721 and +98(913)113-0350, Email:sajedi@med.mui.ac.ir

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Abstract:

Numerous pharmacological interventions had been proposed to treat postoperative shivering. Many opioid derivatives widely used to treat shivering.

Meperidine is a potent opioid which also frequently uses to control shivering after general anesthesia. There are some controversies about the effects of opioid derivatives to control postoperative shivering. This study was a double blind study to compare the effects of fentanyl, sufentanil, alfentanil , tramadol and meperidine on post general anesthesia shivering.

This prospective double blinded and randomized clinical study was performed to compare the antishivering effects among meperidine ,tramadol, fentanyl, sufentanil and alfentanil, in post general anesthesia shivering. One hundred and sixty patients who had shivering Grade III and IV were randomly allocated to one of five groups for intravenous treatment: group M (n=32) received meperidine 0.4 mg/kg, group F (n=32) received fentanyl 0.4μ/kg, group S (n=32) received sufentanil 0.1μ/kg, group T (n=32) received tramadol 0.25mg/kg and group A (n=32) received alfentanil 4μ/kg. The response rate, treatment time, minimal and maximal time to treatment and response duration were measured. Data were analyzed with ANOVA, two sample T test and Pearson correlation test where they appropriated. There were no significant differences among five groups with respect to the response rate, treatment duration, minimal and maximal response time to treatment and duration of treatment (P>0.05).Also side effects, such as purities, nausea, vomiting and dizziness were not significantly different.

We concluded that all five drugs had a similar effect in the treatment of post general anesthesia shivering. Narcotics may be involved other mechanism than opioid receptors to control shivering post operatively.

Key words: Postoperative shivering, pure μ agonist narcotics, Hypothermia.

Introduction:

Hypertension is major health problem affection approximately 20% of Iranian adults [1]. Among the many causes for inadequate blood pressure control in hypertensive patients, poor compliance with long term pharmacologic treatment is the leading one [2]. One year after the beginning of treatment 16-50% of patients fail to continue to take their medications [3, 4].

Shivering is an unpleasant and frequent complication in the postoperative period [1]. In a survey on 33 clinical problems, anesthesiologists ranked postoperative shivering 8th when its frequency was considered and 31st when asked about the importance of preventing this complication [2]. The mechanisms chiefly responsible for Shivering in patients undergoing surgery are intraoperative temperature loss, increased sympathetic tone, pain and systemic release of pyrogens [3]. The metabolic and hemodynamic consequences of shivering include increased expenditure of cardiac and systemic energy, increased oxygen consumption and carbon dioxide production, and increased cardiac work [4].

Shivering may also increase intraocular and intracranial pressure, and it may contribute to increased wound pain [5]. Numerous pharmacological interventions have been proposed for the treatment of post operative shivering [1]. The mechanism of the antishivering effect of these drugs has not been get completely clear [1]. Many opioid derivatives widely used to treat shivering such as meperidine, morphine, fentanyl , alfentanil, sufentanil , butorphanol and tramadol [1]. On the other hand, it has been told meperidine possesses special antishivering properties and prevents or manages shivering far better than roughly equianalgesic doses of other opioids [6,7].May be this effect relates to k-opioid receptors and it is the reason that butorphanol stops shivering better than fentanyl [8,9]. But a recent study said that meperidine is a potent agonist at the α2 adrenoreceptors and antishivering action of meperidine possibility is tranduced by this mechanism [10]. Perhaps other mechanisms other than action on opioid receptors are responsible for antishivering action of opioids. In a systematic review of randomized controlled trials survey, which is done on 20 trials there was not sufficient data about pure μ agonist opioids to control shivering[1]. For these controversies, in this study we compared the antishivering activity of three pure μ agonist opioids (fentanyl,alfentanil and sufentanil)with tramadol and meperidine(most superior at κ receptor) in a double blind study to evaluate these drugs effects on post general anesthesia shivering.

Materials and Methods:

This study was a double blinded, randomized and clinical trial, which was conducted after approval of the local research ethic committee at the Isfahan University of Medical Science and Health Service in 2003. Inclusion criteria were age above 14 years, ASA physical status I to III and presence of shivering grade III or IV. If the patients had a known history of alcohol or substance abuse were excluded from the study. Shivering was graded with a scale similar to that validated by Crossley and Mahajan [11]:0=no shivering, 1= piloerection or peripheral vasoconstriction but no visible shivering, 2 = muscular activity in only one muscle group, 3 = muscular activity in more than one muscle group but no generalized shivering, 4= shivering involving the whole body. Only patients who developed Grade 3 0r 4 shivering were included in the study. Patients were randomized by using computer generated tables to enter in one of 5 studies groups which were: Group M (n=32) received meperidine 0.4mg/kg, group F (n=32)

received fentanyl 0.4μ /kg, group S (n=32) received sufentanil 0.1μ/kg, group A (n=32) received alfentanil 4 μ/kg and group T (n=32) received tramadol 0.25mg/kg. These doses were nearly equianalgesic and were obtained according to previous studies [1, 12, and 13] and also a pilot study for tramadol before starting the study. The preparation of study drugs were done according the computer generated table. During the time of the study, every morning all drugs were diluted so that each milliliter of solutions were become suitable for 20 kg of patient's body weight. All study solutions were colorless and had 5 milliliter volumes. The study solutions were prepared and labeled by one of the researcher and the another researcher were done treatment and observation of the patients. After entering the patients to the recovery room, they were observed by nurses who trained to observe shivering before they entering into the study, and if shivering grades III or IV were observed the patients entered the study. At first the tympanic temperature of the patient was registered with an ear thermometer (OMRON, Gentle temp MC SO. E, MATSUSAKA) and then one of the coded drugs was infused intravenously for the patient. At the same time chronometer was turned on and the time between drugs injection and stopping of shivering (treatment time) was registered. Also the time between treatment and a new shivering period (relapse interval) was registered. All patients were observed during 60 minute after treatment for shivering and any drugs side effects. All drugs side effects also were registered. After collection of all data and opening the codes, data were analyzed with appropriate test. Age and weight were analyzed with one way ANOVA test. Tympanic temperatures at the time of shivering and after shivering between groups were analyzed with ANOVA .Comparison between the two temperatures was analyzed with Paired sample test. Response rate were measured with Chi-Square test and analyzing of another data were done with ANOVA.

Results:

We evaluated 5354 patients; from those, 1767 patients had shivering (31%) and 160 of patients had shivering grade III and IV that enter to the study. There were no statistical differences between five groups for age, weight, sex, ASA physical status and basic tympanic temperature and post shivering temperature (Table 1). There were statistical differences between mean tympanic temperatures before and after shivering(35.7±0.6 versus35.9±0.6 $P<0.001$). Also there were no significant differences among five groups for the response rate (the numbers of patients who stopped shivering after IV treatment), treatment time (the time between injection of the study drugs and shivering control), relapse rate (the number of patient who had shivering after a period of symptom freeing) and relapse interval (the time between stopping shivering and a new shivering period) (Table 2). The numbers of side effects in each group were very low and we did not able to evaluate them statistically (Table 2).

Table 1. Patient characteristics:

Variable	Sufentanil	Fentanyl	Alfentanil	Mepridine	Tramadol	P-value
Age (y)	27.6±12	25.7±11	23.3±8	27.8±13	24.7±10	0.42
Weight (kg)	60.7±11	64.9±11	65.5±15	66.8±13.5	62.3±13	0.32
Sex (M/F)	22/10	27/5	21/11	25/7	23/9	0.44
ASA (I/II)	32/0	31/1	31/1	32/0	31/1	
Shivering grade (III/IV)	17/15	14/18	13/19	15/17	15/17	
Tympanic Temperature I (C)	35.6±0.5	35.7±0.8	35.8±0.7	35.8±0.6	35.8±0.5	0.93
Tympanic Temperature II (C)	35.8±0.7	36.0±0.6	36.0±0.2	36.0±0.2	36.0±0.2	0.98

Table 2: Responses of The patients to the treatments

Variable	Sufentanil	Fentanyl	Alfentanil	Mepridine	Tramadol	P-value
Response rate (n)	25(78.1%)	26(81.2%)	24(75%)	29(90.6%)	26(81.2%)	0.58
Mean Treatment time (second)	70±47	76.4±57	74.4±57	79.4±40	79.8±52	0.94, F=0.195(4,155)
Range of Treatment time (second)	30-150	30-167	36-170	30-146	30-180	
Relapse Interval	24±12	3.3±4.1	6.3±3.2	1.5±1	6.3±3.5	0.5
Relapse rate	7	6	8	3	6	0.06
Side effects (Nausea-Vomiting/ Vertigo/ Others)	2/1/0	2/1/0	2/1/0	0/0/1	4/1/0	

Discussion:

The result of this study indicates that all five drugs (meperidine, alfentanil, sufentanil, fentanyl and tramadol) effectively treat shivering after general anesthesia. The incidence of shivering after general anesthesia was 31% in this study, which is similar the result of other studies [14].The mechanisms chiefly responsible for shivering in patients undergoing surgery are intraoperative temperature loss, increased sympathetic tone, pain and systemic release of pyrogens[3].

Meperidine is a commonly used medication for controlling post anesthetic shivering. The antishivering action of meperidine has previously been attributed to its action on κ-opioid receptors[10]. It may be a reason that nalbuphine controls postoperative shivering as well as meperidine [15]. However, other more K-receptor selective drugs such as pentazocine, failed to inhibit post anesthetic shivering. This finding suggests that k-opioid receptors are not implicated [16].On the other hand, it has been suggested that the effect of meperidine on shivering may be transduced by a potent agonist action of the α2 adrenoreceptors in clinical concentration [10].

Also in another study it has been seen that tramadol and its enantiomers are bound weakly to human μ and K-opioid receptors, but it controls shivering similar to meperidine [17,18].Also it was shown that the antinocioceptive effects of tramadol were significantly decreased by yohimbine and idazexam (both α2 adrenoreceptor antagonist) [19].Therefore other mechanism are probably responsible for anti shivering action of meperidine rather than action on k-opioid receptors.

Some previous studies mentioned that the effect of meperidine on shivering is more effective than that of pure opioid receptor agonists but another study didn't find it [20, 21].

The result of our study is similar as some previous study (1) and against the others [20, 21].The different findings of our study may be explained with new research about receptors which are responsible for antishivering action of meperidine. Another study about meperidine and doxapram belives that there was a dose – dependent increase in the proportion of patients who stopped shivering with meperidine [12]. Further doses-responses and also receptors studies need to evaluate the minimum effective doses of these drugs and the mechanism of anti shivering activity. In this study the incidence of side effects were very low and the differences were not significantly among groups. This was similar to the results of previous study [1].

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