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Original Article

Minimum effective dose of Tramadol in the treatment of postanesthetic shivering

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Abstract

BACKGROUND: To determine the minimum effective dose of intravenous administration of tramadol on controlling postanesthetic shivering (PAS) and frequency of effects.

METHODS: Seventy five patients who had shivering grade III or IV after general anesthesia with isoflurane in the recovery room were included in the study. The patients were divided randomly among five groups to receive the same dose of tramadol: 0.2 mg/kg, 0.4 mg/kg, 0.6 mg/kg, 0.8 mg/kg and 1 mg/kg. The shivering grades, tympanic temperature immediately prior to administering the treatment, time spent to control shivering, shivering relapse, time interval between the two shivering periods and side effects were registered. Data were analyzed with SPSS software, version 14. Chi-square test, t-student test and analysis of variance were used where they were appropriate. P value<0.05 was considered significant.

RESULTS: There were no statistically significant differences among treatment groups with respect to demographic data, duration of anesthesia, room temperature of postanesthesia care unit, shivering grade before treatment and central temperature at the time of treatment. There was no significant difference among the number of patients who stopped shivering with 0.2 mg/kg compared with 1 mg/kg of tramadol. There was no significant difference among the five doses for shivering relapse. Frequency distributions of side effects were not different among the five groups.

CONCLUSIONS: All patients completely stopped shivering with tramadol 0.4 mg/kg or more in 5 minutes after treatment. With 0.2 mg/kg only 80% of patients stopped shivering. Although the difference between 0.2 mg/kg and 1 mg/kg was not statistically significant, because of the limited number of cases we were not able to reject type two errors. According to this study, we suggest 0.4 mg/kg of tramadol for shivering control.

KEY WORDS: Tramadol, postanesthetic shivering, minimum effective dose.

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Postanesthetic shivering (PAS) occurs frequently postoperatively and may be very distressing for patients. Numerous drugs have been used to treat postanesthetic shivering. Intravenous administration of the opioids, meperidine and nalbuphine, the nonopioid analgesic tramadol, the [alpha]$_2$-adrenergic agonist clonidine, the respiratory stimulant doxapram, and the cholinomimetic agent physostigmine have all reduced the incidence of shivering or suppressed established shivering [1]. Tramadol is an antishivering drug, which inhibits the reuptake of 5-HT, norepinephrine, and dopamine and facilitates 5-HT release [1-3]. The most common adverse events are nausea, vomiting, dizziness, headache, sedation, drowsiness, sweating and dry mouth [2,3]. The threshold for seizures is lowered by

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tramadol. In addition, the risk of seizure is enhanced by the concomitant use of tramadol with selective serotonin reuptake inhibitors or neuroleptics, and its use in patients with a recognized risk for seizures, i.e., alcohol withdrawal [3,4]. Side-effects appear to be dose- as well as route-dependent; parenteral administration is associated with more complications [3]. Importantly, unlike other opioids, tramadol has no clinically relevant effects on respiratory or cardiovascular parameters at recommended doses in adults or children [2,3]. Different doses of tramadol from 0.25 mg/kg to 3 mg/kg were used to control postoperative shivering in different studies [1,5-10]. The aim of this study was to compare efficacy of different doses of tramadol in controlling postoperative shivering and frequency of side effects after general anesthesia.

Methods

This study was a prospective, randomized, double blind clinical trial conducted on 75 patients in 5 groups. After approval of the study by local Ethics Research Committee, 75 patients who developed shivering grade III or IV in the recovery room were included in the study [11]. Inclusion criteria were age between 18 and 64 years, ASA class I or II, balanced anesthesia with isoflurane and lower abdomen and extremities surgery with duration of anesthesia between one and three hours. Exclusion criteria were administration of monoamine oxidase inhibitors, previous history of seizure, elevated intracranial pressure, drug abuse or any unpredicted event during anesthesia. All patients who were candidate for balanced anesthesia with isoflurane were controlled for inclusion and exclusion criteria of the study. Induction of anesthesia and maintenance of anesthesia were the same in all patients. Patients received standard postoperative management in the recovery room. Oxygen was administered via a nasal cannula (3 L/minutes) and patients were covered with a cotton blanket. All patients were observed for shivering. If the patients found shivering grade III or IV according to Crossly and Mahajan classification [11], they were enrolled in one of the 5 groups of our study. Each group included 15 patients, receiving the same dose of tramadol: 0.2 mg/kg, 0.4 mg/kg, 0.6 mg/kg, 0.8 mg/kg and 1 mg/kg. Ten ml syringes containing tramadol 0.2%, 0.4%, 0.6%, 0.8% and 1% were prepared by one of the investigators. The preparation of syringes was done according to the computer generated table. The syringes were only labeled with a code and the two other investigators and patients were blinded to the content of each syringe. The two other investigators also assessed the shivering grades, measured tympanic temperature immediately prior to administering the treatment, administered 0.1 ml/kg of the solution intravenously and observed the patients. The tympanic temperatures of patients were measured with an infrared ear thermometer (OMRON, Gentle temp MC SO. E, MATSUSAKA). After injection of each code, the patients were observed for 5 minutes and the time taken to stop shivering was measured with Fortex Chronometer and was recorded. All the patients were observed continuously during the 45-minute period after receiving the study drug for recurrence of shivering and drug side effects. If shivering relapsed, the time intervals between the two shivering periods were registered. If patient shivered 5 minutes after injection of the solution, meperidine 0.35 mg/kg was given. After collection of all data, they were analyzed with SPSS software, version 14. Chi-square test, t-student test and analysis of variance (ANOVA) were used where they were appropriate. P value<0.05 was considered statistically significant.

Results

We evaluated 2677 patients, from that 892 patients had shivering (30%) and 75 patients had shivering grade III or IV who had inclusion criteria for our study. There were no statistically significant differences among treatment groups with respect to age, gender, weight, ASA physical status, duration of anesthesia, room temperature of postanesthetic care unit (PACU) and central temperature at the time of treatment. Also, frequency distribution of

shivering grade before administration of drug was not different among the five groups (table 1). There was no significant difference among the number of patients who stopped shivering with 0.2 mg/kg compared with those who received 1 mg/kg of tramadol (table 2). Response time to treatment was not different among the five groups (table 2). There was no significant difference among the five doses for shivering relapse (table 2). Frequency distributions of side effects were not statistically different among the five groups (table 3). Mean changes of systolic, diastolic and mean arterial blood pressure after medication were not different among the five groups.

Table 1. Demographic data, core temperature, PACU temperature, shivering grade immediately before drug administration and duration of anesthesia.

Drug doses/variable	0.2 mg/kg	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg	1 mg/kg
Age (year)	32.5 ± 14.9	31.9 ± 13.7	34.1 ± 11.9	32 ± 12.6	34 ± 13.3
Weight (kg)	69 ± 11	69.5 ± 7	70 ± 9.5	71.5 ± 10	69 ± 11
Sex (M/F)	10/5	8/7	10/5	9/6	9/6
ASA Class I/II	13/2	12/3	13/2	14/1	14/1
Core temperature (°C)	35.9 ± 0.5	35.6 ± 0.5	35.3 ± 0.6	35.5 ± 0.55	35.3 ± 0.4
Shivering Grade III or IV	9/6	7/8	6/9	10/5	9/6
PACU temperature (°C)	26 ± 0.2	26 ± 0.1	26 ± 0.1	26 ± 0.3	26 ± 0.2
Duration of anesthesia (h)	3 ± 0.2	2.8 ± 0.3	3.1 ± 0.2	3 ± 0.1	3 ± 0.1

P≥0.05 for all data.

Table 2. Time to response and shivering relapse in patients who stopped shivering with different doses of drug.

Variables	0.2 mg/kg	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg	1 mg/kg
Mean time to response in minutes (± SD)	3.16 ± 1.69	2.8 ± 1.17	2.8 ± 1.27	2.71 ± 0.82	2 ± 0.97
Number of response	12 (80%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)
Number of shivering relapse	1 (8.3%)	2 (13.3%)	1 (7.6%)	0 (0%)	0 (0%)

P≥0.05 for all data.

Table 3. Frequency distribution of complications among five groups of study.

Side Effects	0.2 mg/kg	0.4 mg/kg	0.6 mg/kg	0.8 mg/kg	1 mg/kg
Nausea	0 (0%)	1 (6.7%)	2 (13.3%)	1 (6.7%)	4 (26.7%)
Vomiting	0 (0%)	1 (6.7%)	0 (0%)	0 (0%)	0 (0%)
Dizziness	0 (0%)	0 (0%)	0 (0%)	1 (6.7%)	0 (0%)
Sedation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dry mouth	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Sweating	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Headache	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Seizure	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

P≥0.05 for all data.

Discussion

The aim of this study was to find the minimum effective doses of tramadol, so that shivering could be treated adequately with the fewest side effects. In most previous studies demonstrating the efficacy of tramadol in the treatment of postoperative shivering, the dose was chosen empirically. This study showed no sig-

nificant differences among the number of patients who stopped shivering with five different doses of tramadol. However, all patients completely stopped shivering with tramadol 0.4 mg/kg or more in 5 minutes after treatment while with 0.2 mg/kg only 80% of patients stopped shivering. Because of limited number of cases we were not able to reject type two errors. Witte and colleague showed that five minutes after intravenous administration of tramadol, shivering grades were zero in all patients treated with 1or 2 mg/kg and only one patient shivered 5 minutes after 0.5 mg/kg. Tramadol 0.5 mg/kg failed to cease shivering in 4 patients after an arbitrary general anesthesia in their study, but data were not significantly different compared with higher doses. They demonstrated that tramadol 2 mg/kg and 0.5 mg/kg were equally effective in lowering prevalence and severity of shivering after a standardized general anesthesia [1]. Finding of our study was in the same direction with their study. Tramadol may prove particularly useful in patients with poor cardiopulmonary function, including the elderly, the obese and smokers, in patients with impaired hepatic or renal function [2]. In our study, different doses of tramadol did not affect cardiovascular parameters. Wrench and colleague showed a dose-dependent increase in the proportion of patients who stopped shivering with meperidine. They concluded that 0.35 mg/kg of meperidine is the minimum dose required to treat post-anesthetic shivering effectively in 95% of patients [12]. There was no relationship between the dose of doxapram and the proportion of people who stopped shivering in their study. Our study also was not able to find a dose relationship between the given dose of tramadol and the proportion of people who stopped shivering. Although differences among five doses were statistically insignificant, only 80% of patients stopped shivering with 0.2 mg/kg. In order to establish whether this 20% difference between the highest and the lowest doses of tramadol is statistically significant, greater sample size is needed. According to our findings, we suggest that 0.4 mg/kg of tramadol can be used as effective as higher doses for shivering control. Also, according to this study and Wrench's study we can conclude that 0.4 mg/kg of tramadol is as effective as 0.35 mg/kg of meperidine for shivering control [12]. Another study may be needed to confirm this conclusion.

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