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ORIGINAL RESEARCH REGIONAL ANESTHESIA

Tramadol vs. pethidine to control perioperative shivering in cesarean section under spinal anesthesia: a double-blind study

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Abstract

Background & objective: Perioperative shivering after spinal anesthesia for cesarean section is a common and unpleasant complication. Currently pethidine is being used but the search continues to look for other agents with faster action and with fewer side effects. Tramadol is a potential anti-shivering drug with modulation of central thermoregulation.

We compared the efficacy of tramadol versus pethidine in the treatment of perioperative shivering of patients undergoing cesarean section under spinal anesthesia.

Methodology: After institutional ethical review committee approval, 42 patients undergoing cesarean section under spinal anesthesia, who experienced shivering, were randomized into two groups, Group T (n = 21) received 1 mg/kg tramadol and Group P (n = 21) received 0.5 mg/kg pethidine. The outcome measures included the time taken to cessation of shivering after the medication, recurrence of shivering and the incidence of side effects.

Results: The parturients with mean age 30.2 ± 5.2 y and body mass index (BMI) 29.9 ± 4.9 kg/m^2 were recruited with comparable data between the two groups. Median time taken from drug administration until cessation of shivering of the tramadol group was faster than the pethidine group (7 min vs 13 min, P = 0.049). However, there was no significant difference in terms of the number of recurrences of shivering (P = 0.606) and incidence of nausea (P = 0.19) between the two groups.

Conclusion: Intravenous tramadol has faster alleviation of perioperative shivering than intravenous pethidine in the treatment of perioperative shivering.

Key word: Tramadol; Pethidine; Cesarean section; Shivering; Anesthesia, Spinal

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1. Introduction

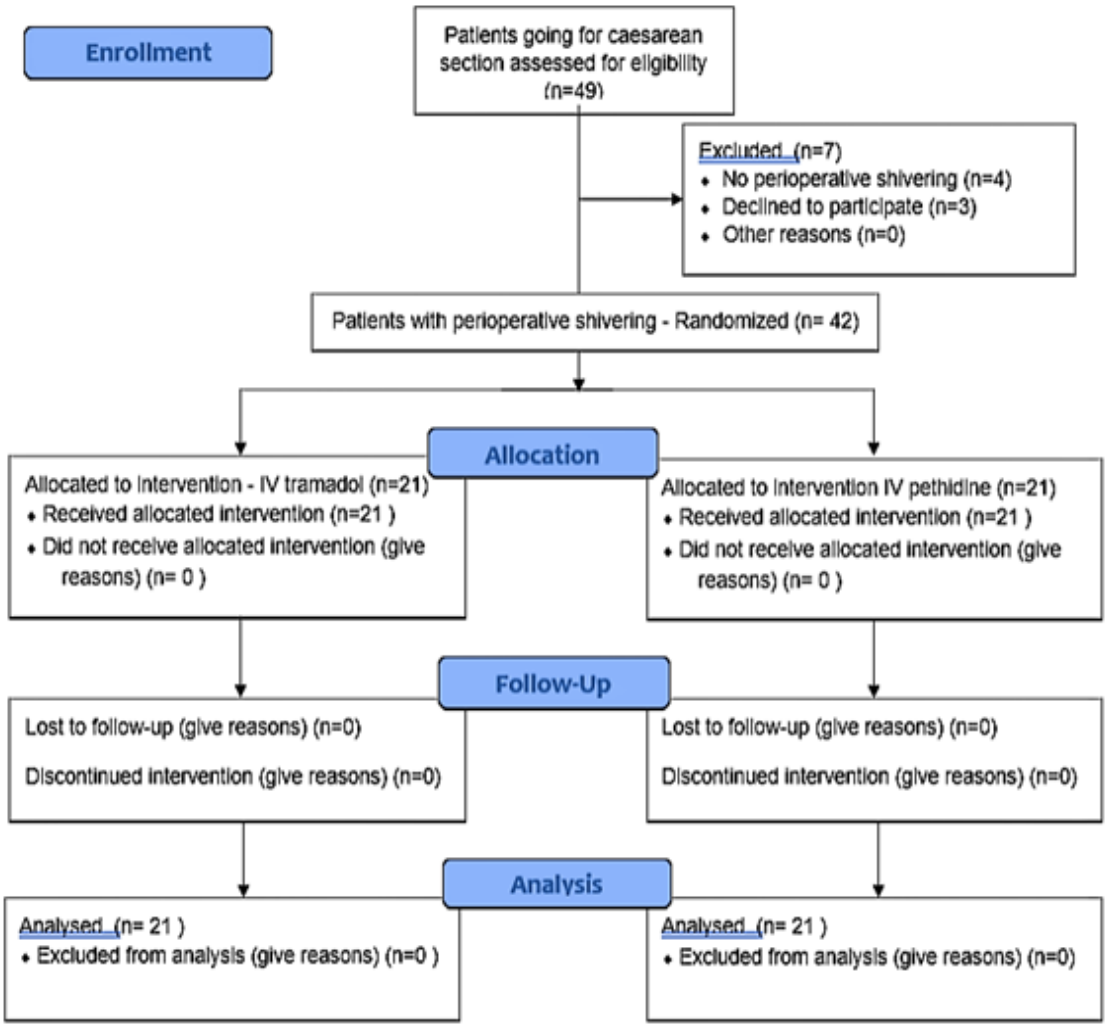

Figure 1: CONSORT flow diagram

Shivering involves skeletal muscles involuntary oscillatory contractions, appearing commonly as a side effect of anesthesia. [1] The causes of perioperative shivering are unclear, but one potential mechanism suggested is acute opioid withdrawal and pain, especially with the use of short action narcotics. [2] Harmful adverse events that may occur due to shivering include an increased heat production in the body by up to six-fold, tripling of oxygen consumption, and other abnormalities like lactic acidosis, hypoxia, hypercarbia, and increased intracranial and intraocular pressure. [3] The incidence of perioperative shivering during cesarean sections can be up to 85%. [4]

Many modalities of treatment are currently employed for the treatment of shivering. Several classes of substances, including N-methyl-D-aspartate (NMDA) receptor antagonists, cations, endogenous proteins, monoamines and cholinomimetics appear to play a role in the shivering control via modulation of central thermoregulatory control mechanisms. [5] The current mainstay of pharmacological treatment in practice is pethidine, which exerts its effect via the opioid receptors. [6] A systematic review found that pethidine was the most effective agent in shivering prevention; however, in the same study they found that the incidence of nausea and vomiting with pethidine was also the highest. [7] Pethidine usage has been associated with several undesirable side effects related to its metabolite norpethidine, including the propensity for epileptic activities. [8]

Tramadol is an analgesic agent and its mechanism of action is through inhibition of the reuptake of 5-hydroxytryptamine-3 (5-HT3) and norepinephrine. [9] These actions have been associated with thermoregulation and have led to its use as an anti-shivering agent. [10] There have been a few studies conducted to test the efficacy of tramadol in the control of perioperative shivering, and the findings of these

studies have shown that tramadol proves to be an effective agent in the treatment of perioperative shivering in the population that has undergone anesthesia and surgery. [11] However, the studies addressing use of tramadol in parturient for shivering in cesarean section have been few and far between. Jayaraj et al. found that the parturients who received intravenous fentanyl, pethidine and tramadol as prophylaxis, had reduced incidence of intraoperative shivering. [12] They also advocated use of low dose tramadol (0.5 mg/kg) as prophylaxis for intraoperative shivering in parturients. Since this particular cohort of

patients have altered pharmacokinetic and pharmacodynamics, the comparison of efficacy and safety of tramadol vs pethidine was necessary. In a previous study only one patient was found with shivering who did not respond to the intravenous tramadol 0.5 mg/kg. [13]

We compared the efficacy of tramadol (1 mg/kg) with pethidine (0.5 mg/kg) for treating perioperative shivering in patients who had undergone cesarean section under spinal anesthesia.

2. Methodology

This randomized, double-blind study was conducted after approval by the Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/19090550). The study included 42 patients aged 18 to 50 y who underwent cesarean section under spinal anesthesia, and which experienced perioperative shivering. Exclusion criteria included patients with allergy to tramadol or pethidine, patients on monoamine oxidase inhibitors, and hemodynamic instability intraoperatively. Written informed consent were obtained from all patients included in the study.

All patients undergoing cesarean sections within the study period were recruited, however only those who had had shivering were randomized. The first 42 patients that experienced perioperative shivering were randomly allocated into one of the two groups; Group T (n = 21) received tramadol 1 mg/kg and Group P (n = 21) received pethidine 0.5 mg/kg for the treatment of shivering. The anesthetist who gave the drugs, the operating theatre nurse who assessed for shivering and the patients were blinded for the study. All patients scheduled for lower segment cesarean section underwent preanesthestic evaluation either in the ward or in the preoperative bay. In the operating theatre, standard monitoring such as non-invasive blood pressure, pulse oximeter and electrocardiography was applied. Vital signs were recorded using GE Datex Ohmeda® Oxy-W4-N monitor. The patient's axillary temperature was recorded using Omron® Digital Thermometer MC-245. The ambient operating room temperature was maintained around 18-22° C as per standard at our institution and monitored using Zeal® Digital Thermo-Hygrometer. A standard spinal anesthesia dose was given in accordance with current practice at our institution: heavy bupivacaine 0.5% according to height (< 150 cm: 1.5 ml; 151-155 cm: 1.5-1.8 ml; 156-160 cm: 1.8-2.0 ml; >160 cm: 2.0 ml), plus fentanyl 15 µg, and intrathecal morphine 100 µg. The Smiths Medical Level 1® Equator® EQ-5000 forced air warmer device was also applied to all of our patients after spinal anesthesia.

Tramadol 10 mg/ml and pethidine 5 mg/ml injection was prepared in 10 ml syringes. The assignment of the content of the syringe was pre-determined using a computer-generated randomization list, and the syringes labelled serially. Once the patient started shivering, the envelope containing the syringe was given to the anesthesiologist to be administered.

The study drug was given after delivery of the fetus, and assessment of timing of shivering cessation was started after administration of the drug. The treatment drug dose was administered based on the patient's weight (0.1 ml/kg) intravenously over 60 sec. Monitoring of the shivering grade and vitals were done by the operating room nurse at 1 min after administration of the study drug, and followed by 5 min interval over the first 30 min and subsequently 10 min interval for 30 min with total duration of assessment for 60 min. Shivering was graded as per Crossley and Mahajan validated scale [Grade 0 = No shivering; Grade 1 = Piloerection or peripheral vasoconstriction

but no visible shivering; Grade 2 = Muscular activity in

only one muscle group; Grade 3 = Muscular activity in more than one muscle group but not generalized; Grade 4 = Shivering all over the body]. [12] Drug efficacy was assessed based on the time taken to cessation of shivering after interventional drug administration and also a decrease in the grade of shivering. Recurrence of shivering after cessation was also assessed. Shivering recurrence was defined as an increase from the shivering grade 0 once grade 0 achieved after administration of the study drug. Side-effects such as changes in the hemodynamic status and nausea and vomiting were also recorded.

The study was completed after one hour of administration of the study drug. Any recurrence of the shivering was recorded. No second dose of the study drug was given in these circumstances. Other complications such as nausea and vomiting were also monitored and treated with intravenous dexamethasone 8 mg and intravenous ondansetron 4 mg. A flow chart for the study is given in Figure 1.

The primary outcome of this study was time taken to cessation of shivering after drug administration.

Table 1: Patient Characteristics in different groups. Data presented as Mean ± SD or n (%)

Variables	All (n = 42)	Pethidine (n = 21)	Tramadol (n = 21)	p-value*
Age (y)	30.2 ± 5.3	29.7± 5.7	30.9 ± 5	0.458
Height (cm)	155.8 ± 5.5	156.2 ± 4.8	155.4 ± 6.2	0.638
Weight (kg)	72.5 ± 12.2	73.7 ± 10.2	71.3 ± 14.1	0.529
BMI (Kg/m^2)	29.9 ± 4.9	30.3 ± 4.6	29.5 ± 5.2	0.587
Type of operation				
Elective	29 (69.1)	16 (76.2)	13 (61.9)	0.317
Emergency	13 (30.9)	5 (23.8)	8 (38.1)	
Comorbidity				
No	20 (47.6)	9 (42.9)	11 (52.4)	0.537#
Yes	22 (52.4)	12 (57.1)	10 (47.6)	
Room Temperature (°C)	20.3 ± 0.85	20.3 ± 0.8	20.2 ± 0.9	0.831#
Patient Body Temperature (°C)	36.0 ± 0.8	36.1 ± 0.6	35.9 ± 0.8	0.313
Mean Arterial Pressure (mmHg)	75 ± 0.9	74 ± 1.9	76 ± 0.4	0.817

**Independent T- test, significant p value ≤0.05 #Chi-square test, significant p value ≤ 0.05*

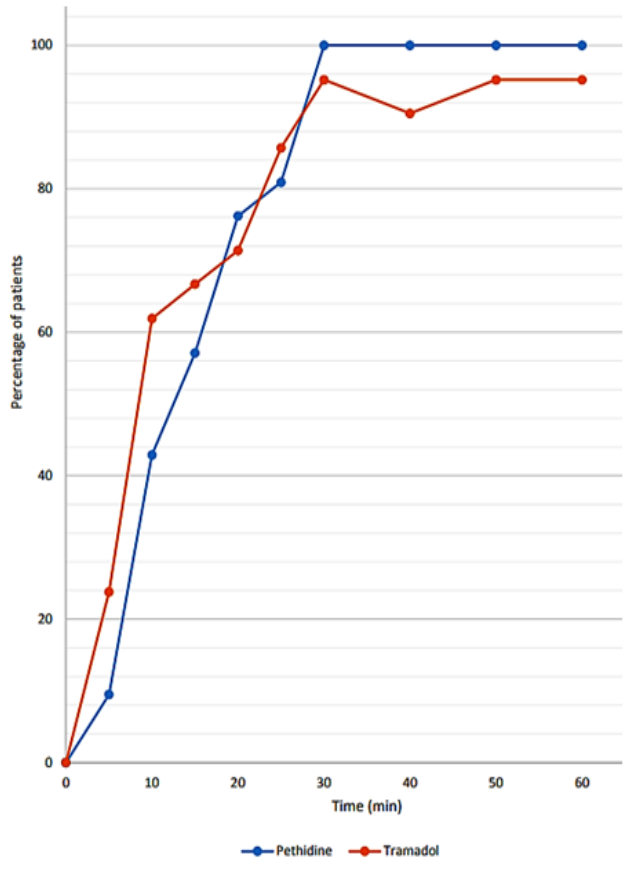

Figure 2: Percentage of patients without shivering at different time points in two groups (n=42)

Secondary outcome measurements included grade of shivering after the treatment, recurrence of shivering after cessation, and the side effects of the study drugs.

Based on a previous study, we used uncorrected chi-squared statistics to calculate the sample size with significance level of 0.05 and the power of study set at 80%. Rate of recurrence in the pethidine group was 23%. [11] The group ratio between tramadol and pethidine was set to 1. Therefore, the estimated sample size needed was 38 patients. Taking into account a 10% drop-outs, we concluded that 21 patients per group were required to prove the hypothesis.

Statistical Analysis

All data were entered and analyzed using STATA version 12.0 (STataCorp, College Station, Texas, USA). Demographic and clinical characteristic of the patients were presented using descriptive statistics in Mean ± Standard Deviation for numerical data and number (percentage) for categorical data. We used Wilcoxon Rank Sum Test to compare the median time to shivering cessation between the two groups, and Fisher Exact test to compare recurrence of shivering. The significance level was set to $P \leq 0.05$.

3. Results

42 patients were included in the study and divided into 21 patients in Group T (tramadol) and 21 patients in Group P (pethidine). Baseline characteristics of the two groups were comparable to each other in terms of

Table 2: Comparison of pethidine and tramadol administration time and time to stop shivering

	Pethidine (n = 21)	Tramadol (n = 21)	z statistic	p value
Time taken to administer study drugs from onset of shivering (min); median (IQR)	6 (3-14)	5 (3-10)	0.594	0.552*
Time taken to stop shivering after administration of study drugs (min); median (IQR)	13 (10-18)	7 (4-17)	1.966	0.049*
Recurrence of Shivering; n (%)	3 (14.3)	1 (4.8)		0.606[a]

**Wilcoxon Rank Sum Test; [a]Fisher Exact Test*

Table 3: Median shivering grade across time between pethidine and tramadol

Time (min)	Pethidine (n = 21)	Tramadol (n = 21)	z statistic*	p value
1	3 (2.3)	2 (2.2)	3.66	0.001
5	2 (1.2)	1 (1.2)	2.3	0.022
10	1 (0.1)	0 (0.1)	0.88	0.379
15	0 (0.1)	0 (0.1)	0.455	0.649
20	0 (0.1)	0 (0.1)	−0.428	0.649
25	0 (0.0)	0 (0.0)	0.409	0.683
30	0 (0.0)	0 (0.0)	−1	0.317
40	0 (0.0)	0 (0.0)	−1.432	0.152
50	0 (0.0)	0 (0.0)	−1	0.317
60	0 (0.0)	0 (0.0)	−1	0.317

**Mann Whitney U Test*

Table 4: Side effect frequency between tramadol and pethidine (n=42)

Side effect	All (n = 42)	Pethidine (n = 21)	Tramadol (n = 21)	p value
Nausea	14 (33.3)	9 (42.9)	5 (23.8)	0.190#
Headache	1 (2.4)	0 (0)	1 (4.8)	0.500*
Dizziness	2 (4.8)	0 (0)	2 (9.5)	0.244*

*# Pearson Chi Square Test; *Fisher Exact Test*

age, weight, operating room temperature and baseline body temperatures (Table 1).

The patients in the tramadol group had a statistically significant faster cessation of shivering time at 7 min compared to patients of the pethidine group at 13 min. (P = 0.049, Table 2). Only 1 patient in the tramadol group experienced a recurrence in shivering compared to 3 patients in the pethidine group (P = 0.606, Table 2).

When analyzed at specific time points there was no statistically significant difference in the proportion of patients who had stopped shivering between the two groups (Figure 2). However, one subject in tramadol group persistently had shivering beyond the study period (Figure 2). Median grade of severity of shivering between the two groups was significantly lower in tramadol group at 1 min and 5 min after administration of study drug. (Table 3).

A total of 14 patients (33%) experienced nausea. A higher incidence was noted in the pethidine group, but the difference was not significant [9 (42.8%) vs 5 (23.8%), P = 0.19]. There were other side effects such as headache and dizziness noted in the tramadol group and none were noted in the pethidine group (Table 4). No major hemodynamic disturbances were noted in either groups and vitals profile were similar between the two groups.

4. Discussion

The etiology of perioperative shivering remains uncertain to this day, however multiple mechanisms of perioperative shivering, both thermoregulatory and non-thermoregulatory, has been proposed and researched including mode of anesthesia (general vs neuraxial, spinal vs epidural) temperature of injectate during neuraxial anesthesia and the usage of opioids. [14]

Extensive literature review has identified many studies done into looking different agents used to either prevent or to treat shivering in parturients undergoing cesarean section. A systematic review done by Liu J et al. found that agents such as dexmedetomidine, fentanyl, sufentanil, tramadol and pethidine effectively reduced the incidence and severity of shivering. [15] Most studies that are available looked into the prevention of shivering by administering the agents before shivering has occurred and investigates the incidence and severity of shivering thereafter, as compared to this study which evaluates these drugs as a treatment agent.

The risk factors responsible for shivering in parturients undergoing cesarean sections may be intraoperative fluid and body heat loss, excitation of the sympathetic nervous system, or response to pain. [16] For this study, intraoperative heat loss was minimized by application of forced air warmers and blankets, thus reducing the variables for shivering. The mechanism by which tramadol exerts its effect on shivering still remains a mystery. Tramadol is a racemic mixture composed of isomers R and L, each exhibiting a distinct activity spectrum. R-tramadol shows weak attraction to μ receptors, 5-OH tryptamine and inhibits "re-uptake" of noradrenaline and eases its excretion. L tramadol inhibits "re-uptake" of noradrenaline. [17] It is possible that the action of tramadol on the sympathetic nervous system plays a role in the control of shivering as this was one of the proposed mechanism of causes for perioperative shivering.

Pethidine has been the leading agent of choice in the treatment of shivering, but it is also associated with undesired side effects of nausea, vomiting, itchiness, and respiratory insufficiency. [18] In our study we found the incidence of nausea was 33% overall in both groups and affecting 42.9% of those receiving pethidine.

The findings of our study have supported previous research findings that has exhibited the superiority of tramadol against pethidine for the treatment of perioperative shivering. In our study, the time until cessation of shivering is shorter in the tramadol group (7 min vs 13 min, $P < 0.05$). Comparing this to the findings of Dhimar et al., they have noted an even quicker time of cessation of shivering at 1 minute for tramadol versus 3 min for pethidine, using a similar dose of tramadol but double the dose of pethidine than our study. [19] We postulate the possible explanation for longer in time for cessation of shivering because our study only involves parturients who relatively have altered pharmacokinetics as compared to general population. Jayaraj et al. found tramadol prophylaxis for shivering with half of the dose (0.5 mg/kg) that given in our study was efficient in preventing incidence of intraoperative shivering while maintain patient's comfort. [12] Since Jayaraj's study is more for prophylactic approach, the dose required for prevention is expected to be lower than a treatment dose. However, the exact lowest dose for treatment of intraoperative shivering in a parturient under central neuraxial blockade is yet to be determined. There is always room for further study involving populations with altered pharmacokinetic such as obese and elderly patients.

: Percentage of patients without shivering at different time points in two groups (n=42)In terms of rate of recurrence, we have found that recurrence of shivering in the tramadol group was lower, in agreement with the findings of both Bhatnagar et al. and Dhimar et al. [11, 19] However in our study, we found that the difference in the rate of recurrence between the two groups to not be statistically significant. For side effect profile, incidence of nausea was higher in the pethidine group, however we noted that the prevalence of nausea in the tramadol group were up to nearly four times the rate seen in previous studies (23.8% vs 6.6%). [19] Possible explanation of this is that the population represented in our study are specifically obstetric patients compared to a more diverse patient group in other studies, and the higher likelihood for nausea in obstetric patients may be attributed to gastrointestinal dysmotility due to alteration in the lower esophageal sphincter pressures in relation to hormonal pregnancy changes and various other metabolic and endocrine differences during pregnancy. [20] An improvement identified is to conduct a multicenter study to capture a more diverse population. In our center, there is a preponderance for the Malay population which might also have genetic influence towards pharmacodynamic response of the drugs. However, this does not accurately represent the heterogeneity that exists in the actual multiracial Malaysian population.

Suggestions for future studies is to test lower doses of tramadol to identify the lowest possible tramadol dose that is still efficacious in the treatment of shivering particularly in specific patients group, i.e; parturient, obesity and elderly. With a lower dose of tramadol, we can expect the incidence of undesirable side effects such as nausea can be reduced. Possible suggestions for other agents to do research on is ondansetron, which has shown anti-shivering properties[21], and if used in combination with tramadol has potential to reduce incidence of nausea and vomiting associated with its

usage. Different additive to the central neuraxial blockade might also have influence towards prevention and treatment of post spinal anesthesia shivering.

5. Limitations

This study had a small sample size and it does not reflect the whole population since our subjects involved only one specific section of the population. A large multicenter study involving parturients with multiple ethnic background, multiple comorbidities with complex medical history and varying age groups would give better reflection towards the optimal dose of drugs to treat perioperative shivering.

6. Conclusion

Based on the results of our study, we conclude that intravenous tramadol 1 mg/kg provides faster relief compared to intravenous pethidine 0.5 mg/kg in the treatment of perioperative shivering. However, the comparative differences in the incidence of recurrent shivering and the side effects were not statistically significant between the groups.

7. Funding

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8. Data availability

The numerical data related to the study is available with the authors on request.

9. Conflict of interest

No conflict of interest was declared by the authors.

10. Author contribution

All authors participated in the concept, conduct of the study, data collection, literature search and manuscript preparation.

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