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Anti-shivering effect of intrathecal tramadol versus intravenous tramadol in patients Received spinal anesthesia for lower limb surgery. A randomized controlled clinical trial

Eman Mohammed Abd El Azeem, Mohamed Emad El-Din Abdel-Ghaffar and Shimaa A. Al-Touny

Anesthesia and ICU, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

ABSTRACT

Background: Shivering occurs in 40–60% of patients under spinal anesthesia. Prophylaxis with intravenous tramadol produces a dose-dependent reduction in the incidence of shivering. Intra thecal Tramadol is used safely as an adjuvant in a dose up to 20 mg. Few studies tested the anti-shivering efficacy of intrathecal tramadol. However, no study compared the anti-shivering effect of the two different routes of tramadol. The aim is to compare the anti-shivering effect of intrathecal versus intravenous tramadol. This study was a randomized, triple-blinded parallel-design clinical trial, conducted in orthopedic operating room in our university hospital

Material and Methods: The study included 86 patients of ASA I & II aged 18 years or more who underwent lower limb orthopedic surgery that lasted less than 2 hours under spinal anesthesia. Patients were randomly allocated into two equal groups: control intravenous (IV) group and interventional intrathecal (IT) group. We used Amadol ampoules 100 mg/2 ml (Adwia company).

Intervention: The control group received IT 15 mg bupivacaine and then IV tramadol 0.25 mg/kg in 5 ml normal saline. The interventional group received 20 mg IT tramadol added to 15 mg bupivacaine then IV 5 ml normal saline. The patients were observed for intraoperative shivering, the primary outcome. Intraoperative hemodynamics, postoperative shivering, and its score were all recorded. Postoperative complications such as nausea, vomiting, and hypotension were documented.

Results: Intraoperative shivering was observed in 18.6% of the patients in IV group compared to 4.6% of patients in the IT group with a P-value of 0.047.

Conclusions: IT tramadol is more efficient in preventing post-spinal shivering compared to IV tramadol.

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1. Introduction

Shivering is a commonly reported complication of spinal anesthesia, reported in 40% to 60% of patients who were anesthetized by subarachnoid (spinal) block [1].

Various drugs like pethidine, clonidine, dexmedetomidine, ondansetron, granisetron, ketamine, and tramadol, were used as anti-shivering. They are simple, cost effective and readily available. [2–4] Tramadol is μ receptor agonist that has anti-shivering effect. It suppresses the reuptake of norepinephrine and 5-hydroxytryptamine (5-HT) and facilitates the release of 5-HT. This pharmacological mechanism of tramadol is proposed to be useful for the thermoregulation process. [5] Tramadol is usually used intravenously for prophylaxis and management of post-spinal shivering in a dose ranged from 0.25 mg/kg to 1 mg/kg [4,6]. It is also a common IT adjuvant, safely used in a dose up to 20 mg to prolong the duration of sensory block, motor block, and postoperative analgesia. [7] Anti-shivering effect of intrathecal tramadol was compared in different doses and with placebo but not compared with IV Tramadol. So, our study focused on comparing the anti-shivering effect of two different routes of tramadol (IV and IT) in patients undergoing lower limb orthopedic surgeries. We assumed that IT route might be more effective than IV route in preventing shivering and decreasing the need of systemic drug for managing shivering. Our primary outcome was comparing the efficacy of IV versus IT tramadol in prophylaxis of post-spinal shivering measured by the incidence of intraoperative shivering. The secondary objectives were the incidence of postoperative shivering and postoperative complications as nausea, vomiting and hypotension.

1.1. Patients and methods

This study was a randomized, controlled triple-blinded parallel-design clinical trial. After obtaining our institutional ethical committee approval, the study proposal was registered at PACTR. The study was conducted in our university hospital, and data were collected in the period from August 2020 to January 2021.

The target population was patients who have been planned for lower limb surgery, which lasted less than 2 hours under spinal anesthesia. The inclusion criteria were both male and female ASA I or II patients, age

CONTACT Shimaa A. Al-Touny shimaa_touny@yahoo.com

more than 18 years, and body mass index less than 40. Exclusion criteria are as follows: those who had uncontrolled or complicated chronic illnesses, skin infection at the site of puncture, bleeding disorders, neuropsychiatric disorders, sepsis, spinal deformities, or those who were on chronic opioid medication. Patients who had a known history of allergy to the local anesthetics or tramadol were also excluded. The sample size was calculated using G power software. Based on the incidence of shivering that was 39.4% when I.V tramadol [8] was used versus 6.67% when IT tramadol [7] was used, the difference between the 2 groups was elicited at an alpha level of 0.05 and a power of 95%. The total sample size was 86 patients divided into 2 groups equally in a ratio of 1:1.

The procedure was explained to the patients, and written informed consent was obtained. Patients were allocated randomly into the control IV group and the interventional IT group. The control group received IT 3.4 ml (15 mg bupivacaine + 0.4 ml normal saline) then IV tramadol 0.25 mg/kg in 5 ml normal saline. The interventional group received 20 mg IT tramadol (in 0.4 ml) added to 15mg bupivacaine (3.4 ml) and then IV 5 ml of normal saline. Randomization was done using a computer-randomizing website and a randomization sequence that was concealed in closed numbered envelopes. One of the anesthesia team, who was not involved in the study, opened the patient's envelope to know the group assignment and prepare the medications, and gave it to the investigator to perform the spinal anesthesia. The patients and the physician who observed the patients were blinded to the group assignment.

The operating room temperature was adjusted between 22to 24 degree Celsius. One peripheral venous cannula was inserted, and all patients received warmed 500 ml of ringer's acetate as co-load. Standard intraoperative monitoring with an electrocardiogram (ECG), non-invasive arterial blood pressure, pulse oximetry, and axillary temperature probe was used. Then, patients received spinal anesthesia in a sitting position at L2-3, L3-4, or L4-5 using a 25 Gauge Quincke needle with a paramedian approach.

Maintenance fluid was calculated and warmed before infusion. Intraoperative hemodynamics were recorded until the end of surgery. Intraoperative shivering and its score were recorded using the Bedside Shivering Assessment Scale (BSAS), [9] which has 4 grades; 0 – None: No Shivering, 1 – Mild: Shivering localized to neck or thorax, it may be observed only as ECG artifact or felt by palpation, 2 – Moderate: Intermittent involvement of the upper limbs +/- thorax and 3 – Severe: Generalized shivering or sustained upper/lower limb shivering. Shivering grades 2 and 3 were managed by an incremental dose of 0.25 mg/kg IV tramadol for both groups with a maximum dose of 100 mg.

Postoperative hemodynamics and shivering were monitored for 24 hours. Postoperative shivering was managed by assuring and warming the patient. IV tramadol was needed if shivering persisted in a titration dose of 0.25 mg/kg IV tramadol with a maximum dose of 100 mg. Paracetamol 1 gm infusion was given to all patients regularly every 6 hours to control the postoperative pains.

1.2. Statistical analysis

All the statistical analysis were performed using Statistical Package for Social Science version 22 (SPSS Inc., Chicago, IL, USA)

Descriptive data were generated for all variables. Median and interquartile range (IQR) were used to describe the continuous data (age, body mass index) as the normality assumption was not met, Normality was checked by using Kolmogorov–Smirnov, while frequencies and percentages summarized the categorical data

As the continuous variables did not follow the normal distribution, the Mann-Whitney U test was used to compare them across groups, while the Pearson Chi–square and Fisher's Exact test was used to compare categorical data across groups as appropriate, $P < 0.05$ is considered statistically significant

2. Results

The study was conducted in the orthopedic operating room in our university hospital in the period from August 2020 to January 2021.

A CONSORT flow diagram shows patients' enrollment in the study Figure 1, in which 95 patients were assessed for eligibility. Nine patients were excluded as 6 patients did not meet the inclusion criteria and 3 patients refused to participate. Analysis of collected data for 86 patients was performed.

Patients' characteristics for both groups were comparable, Table 1.

The incidence of intraoperative shivering was higher in the IV group (18.6%) compared to 4.6% in the IT group, while, the severity of shivering in both groups was comparable (P-value = 0.88), Table 2.

The incidence of postoperative shivering in the IT group was lower (7%) than in the IV group (21%) with p-value = 0.045, Table 3. However, the severity of postoperative shivering was comparable between both groups.

The reported complications in both groups were nausea, vomiting and hypotension. It was found that patients who were administered IT tramadol had lower incidence of nausea 9.3% than those in IV group 27.9%. On the other hand, there was no statistically significant

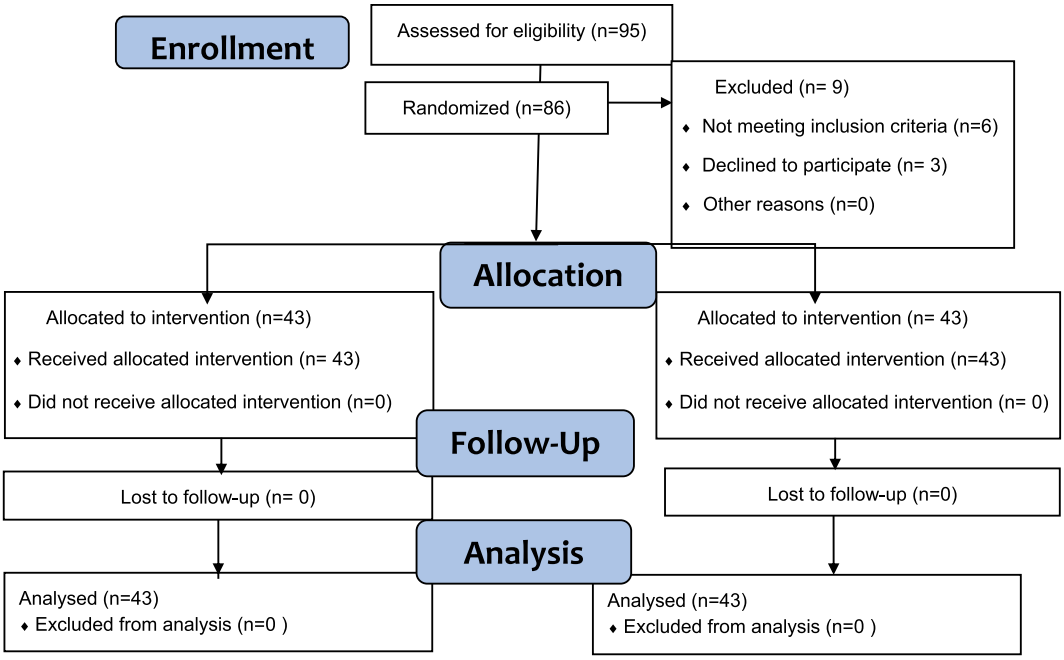

Figure 1. Consort flow diagram

difference in the incidence of vomiting (p = 0.39) or hypotension (p = 0.21) between both groups, Table 4.

3. Discussion

Many clinicians searched for prophylaxis of post-spinal shivering. IV tramadol is usually used for prophylaxis and management of post-spinal shivering. It was used intravenously in a dose range from 0.25 to 1 mg/kg and showed efficacy in controlling shivering with side effects increasing with larger dose. [4,6,10–14]

Also, IT tramadol was commonly used as an additive to local anesthetic in a dose up to 20 mg to prolong the duration of sensory block, motor block, and post-operative analgesia. [15–17]

The anti-shivering mechanism of Tramadol is explained by its μ receptor agonist effect. It suppresses the reuptake of serotonin, norepinephrine, and 5-hydroxytryptamine (5-HT) at the level of the spinal cord and facilitates the release of 5-HT. It has a role in the thermoregulation process. [5] Using a single IT tramadol dose is supposed to alleviate the need of giving further systemic doses for controlling shivering. So, protecting the patients from the systemic side-effects of the drug. [7]

Previous studies [5,7,18–21] compared IT tramadol in different doses, with a placebo or with other drugs to test its anti-shivering effect. However, no one compared the effect of the 2 different routes of tramadol on prophylaxis of post-spinal shivering. So, this research was designed to assess the prophylactic effect of IT tramadol in a dose of 20 mg versus 0.25 mg/kg IV tramadol on decreasing the incidence of shivering. Our primary outcome was comparing the efficacy of IV versus IT tramadol in the prophylaxis of post-spinal shivering. The secondary objectives were the incidence of postoperative shivering and postoperative complications such as nausea, vomiting, pruritus and hypotension.

Patients who received IT tramadol 20 mg were statistically significantly associated with lower incidence of intraoperative shivering than those who received 0.25 mg/kg IV tramadol (4.6% VS 18.6%) with P-values < 0.0.47.

However, the severity of shivering was comparable in both groups (P-value = 0.88). Moreover, it was found that patients on IT tramadol were statistically significantly associated with a lower incidence of postoperative shivering, and only 3 patients (7%) experienced shivering in the IT group compared to 9 patients (21%) in the IV group (p = 0.047).

Gupta and Gupta [7], Badhe et al. [19], and Bansal et al. [5] studied the effect of IT tramadol on post-spinal shivering intraoperatively. Gupta and Gupta compared the IT dose of 20 mg (G T20) with 10 mg (G T10) versus placebo (GP), while Badhe et al. and Bansal et al. tested the anti-shivering effect of 20 mg IT tramadol versus placebo.

The results of Gupta and Gupta show that the incidence of shivering was significantly reduced in G T10 versus GP (20% vs. 53.33%) and G T20 versus GP (6.67% vs. 53.33%) and comparable in both doses of tramadol. So, the incidence of shivering in Gupta and Gupta's study 6.67% is near to our results 4.6%.

Badhe et al. and Bansal et al. found that the incidence of shivering in the IT tramadol group was 0%

Table 1. Comparison between the two groups regarding patients' characteristics (demographic data; age, sex, BMI and chronic illness).

Variables	Type of tramadol administration: Intravenous tramadol (n = 43)	Intrathecal tramadol (n = 43)	p-value
Age (years), median(IQR)	46(21)	55(28)	0.10 [a]
Sex, n (%)			
Male	24 (56.5)	26 (60.4)	0.66 [b]
Female	19 (43.5)	17 (39.6)	
BMI (kg/m^2), median(IQR)	**24.8(6.3)**	**27.7(6.9)**	0.26 [a]
History of chronic illness n (%)			
Absent	25 (58.1)	29 (67.5)	0.37[b]
Present	18 (41.8)	14 (32.5)	

Variables presented as Median and interquartile range (IQR) or patients' number and percent as appropriate, [a] *p-values are based on the Mann-Whitney U test.* [b] *p-values are based on the Chi-square test. Statistical significance at P < 0.05*

Table 2. Intraoperative shivering (number of patients) in both groups.

Comparison between the two groups in regard to intraoperative shivering

Variables	Type of tramadol administration: Intravenous tramadol (n = 43)	Intrathecal tramadol (n = 43)	p-value
Incidence of shivering	**N (%)**	**N (%)**	
Absent	35 (81.4)	41 (95.4)	**0.047 b***
Present	8 (18.6)	2 (4.6)	
Shivering score	**N (%)** (n = 8)	**N (%)** (n = 2)	
0 – None	0 (0)	0 (0)	0.88[a]
1 – mild	2 (4.65)	1 (2.3)	
2 – moderate	4 (9.3)	0 (0)	
3 – severe	2 (4.65)	1 (2.3)	

Variables are presented as patients' number and percent,[a]*p-values are based on Fisher's exact test.* [b]*p-values are based on chi-square test, *Statistical significance as P < 0.05*

and 6.66%, respectively. This incidence is close to ours 4.6%.

Subedi et al. [21] compared IT 10 mg tramadol to fentanyl and recorded that intraoperative shivering was 5% in the IT group. Despite the lower dose used, it is almost similar to ours 4.6%

To our knowledge, no study tested the prophylactic effect of IV tramadol in the dose of 0.25 mg/kg. But this dose was used for the treatment of the witnessed intraoperative shivering. However, larger doses were used for prophylaxis of intraoperative shivering.

Chan et al. [5] used IV tramadol in a dose of 0.25 mg/kg in the treatment of shivering to compare that dose with tramadol 0.5mg/kg and saline and found that the response to treatment was effective in 92%, 80% ,and 27%, respectively. Moreover, Chan et al. concluded that the two doses of tramadol were equally effective in treating intraoperative shivering. In our study, the response of prophylaxis was effective in 81.4% of the patients and the incidence of shivering was 18.6%. The difference between the two studies is that Chan et al. used tramadol as treatment, while we used it as prophylaxis of shivering. Despite this difference, the incidence of intraoperative shivering is comparable.

Kaya et al. [12] compared IV tramadol in a dose of 0.25 mg/kg to meperidine for the treatment of intraoperative shivering. They tested the response of

Table 3. Incidence of postoperative shivering.

Variables	Type of tramadol administration: Intravenous tramadol (n = 43)	Intrathecal tramadol (n = 43)	p-value
Incidence of postop. shivering	N (%)	N (%)	
Absent	34 (79)	40 (93)	**0.045 a***
Present	9 (21)	3 (7)	
Shivering score	**N (%)** (n = 9)	**N (%)** (n = 3)	
0 – None	0 (0)	0 (0)	0.71[a]
1 – mild	5 (11.66)	2 (4.66)	
2 – moderate	3 (7)	1 (2.33)	
3 – severe	1 (2.33)	0 (4.66)	

*Variables are presented as patients' number and percent, p-values are based on Fisher's exact test. *Statistical significance as P < 0.05*

Table 4. Postoperative complications among the two groups.

Variables	Type of tramadol administration: Intravenous tramadol (n = 43)	Intrathecal tramadol (n = 43)	p-value
Nausea			
Present	12 (27.9)	4 (9.3)	**0.026[b]***
Absent	31 (72.1)	39 (90.7)	
Vomiting			
Present	4 (9.3)	2 (4.6)	0.39 [b]
Absent	39 (90.7)	41 (95.4)	
Hypotension			
Present	2 (4.6)	3 (7)	0.21 [b]
Absent	41 (95.4)	40 (93)	

Variables are presented as patients' number (percent), [a] *p-values are based on Fisher exact test.*
p-values are based on chi-square test, Statistical significance at P < 0.05

patients shivering to the treatment and found that it was effective in 90% of the patients. This is similar to our results that reported an incidence of shivering 18.6%, while 81.4% of the patients did not report intraoperative shivering.

Nnachetaet al. [8] compared the prophylactic effect of I.V tramadol 50 mg (Group T) to ondansetron on post-spinal shivering and observed an incidence of 39.4% in Group T. This incidence is relatively higher than our results (18.6%). This may be due to the difference in the target population. Nnacheta et al. worked on women who underwent cesarean section (C.S), while our study included both sex in orthopedic surgery. Both the female population and the nature of surgery (C.S) are risk factors for anxiety that may increase shivering. Also, the hypotension induced by spinal anesthesia is more in parturient due to the increased intra-abdominal pressure. Therefore, hypotension increases the incidence of shivering [22].

The authors who used the same doses as our study did not record the incidence of postoperative shivering. Studies that followed up postoperative shivering are limited. Subedi et al. [21] studied IT tramadol in a dose of 10 mg and found that postoperative shivering occurred in 3%. Compared to our results (7%), these are nearly comparable.

The most commonly reported complications in both groups in our study were nausea, vomiting, and hypotension. It was found that patients who were administered IT tramadol had a lower incidence of nausea (9.3%) than IV the tramadol group (27.9%) (P value = 0.026). Moreover, there was no statistically significant difference in the incidence of hypotension (p = 0.21) and vomiting (p = 0.39).

Gupta and Gupta [7] reported that the most common side effects were nausea, vomiting, and hypotension. Moreover, a dose-dependent response with an insignificant increase in the occurrence of perioperative nausea and vomiting was recorded with an increasing dose of IT tramadol (20 mg). The incidence of nausea 6.67% is close to ours 9.3%.

Bansal et al. [5] showed that 26.66% of the patients in the IT group had nausea. This incidence is relatively higher than ours (9.3%). This may be due to the younger age, lower weight than ours, and the nature of the cesarean section surgery in which visceral and peritoneal manipulation occurs. Moreover, the parturient population has a higher incidence of nausea and vomiting [23] than orthopedic patients.

So, we concluded from this study that adding IT tramadol in a dose of 20 mg to local anesthetic is more efficient in preventing post-spinal shivering compared to IV tramadol in a dose of 0.25 mg/kg with less side effects in the IT tramadol group.

4. Limitations

Our study was applied to a specific population, ASA I &II, BMI less than 40, and on one type of surgery, orthopedic Our study tested a single IT dose. So, to generalize the results of our study, more studies are needed to be performed on different population groups, as patients with BMI more than 40, patients with comorbidities, older age, or other types of surgery. Also, the anti-shivering effect of different doses of IT tramadol should be tested to detect the optimum dose that prevents shivering with minimal or no side effects

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Disclosure statement

No potential conflict of interest was reported by the authors.

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