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Original Research Article

COMPARING THE EFFECTS OF LOW DOSES OF KETAMINE AND TRAMADOL IN THE PREVENTION OF POST-SPINAL ANESTHESIA SHIVERING IN CESAREAN SECTION

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Abstract: *Post-spinal anesthesia (SA) shivering is a common complication following cesarean section (CS) and can pose various challenges for both patients and healthcare providers. Pethidine has been the standard treatment for this issue, but it is not recommended for nursing mothers. This study aimed to compare the efficacy of low-dosage tramadol (T), ketamine (K), and a placebo (P) in managing post-SA shivering in pregnant women undergoing CS. The objective of this study was to evaluate and compare the frequency and intensity of shivering in post-CS patients treated with low-dosage tramadol, ketamine, or placebo. Additionally, we sought to assess the impact of shivering on patients and draw conclusions about the most effective medication for shivering management in this context. A randomized, double-blind trial was conducted at the tertiary care hospital in Lahore, Pakistan, from February 2019 to December 2020. A total of 180 pregnant women undergoing CS with SA were enrolled and randomly assigned to one of three groups: tramadol (T), ketamine (K), or placebo (P). The study-maintained uniformity in the demographic characteristics of all patients. The frequency and intensity of post-SA shivering were recorded, and these observations were compared among the three groups. The results of this study revealed significant differences among the three groups regarding the incidence and intensity of post-SA shivering. Shivering was observed in 33 (55.0%) patients in the ketamine (K) group, 12 (20%) in the tramadol (T) group, and 39 (65%) in the placebo (P) group (P = 0.0001). Tramadol demonstrated the highest efficacy in managing post-SA shivering, followed by a lower dosage of ketamine (K). The high incidence of shivering in the placebo group emphasized the necessity for preventive shivering management strategies in the context of CS under SA. Based on the results it can be concluded that the low-dose tramadol and ketamine are effective in reducing shivering frequency and intensity compared to a placebo. They can be considered as alternative options for nursing mothers who face challenges with pethidine. Proactive measures are recommended to manage post-SA shivering for better patient outcomes following CS under SA.*

Keywords: Cesarean Section, Ketamine, Tramadol, Shivering, Spinal Anesthesia

Introduction

Spinal anesthesia (SA) is the preferred choice over general anesthesia (GA) during cesarean section (CS) due to its early onset, ease of use, and multiple benefits, including avoiding possible neurological damage caused by GA (Sedighinejad et al., 2019). However, shivering is a common and undesirable side effect of SA in pregnant women undergoing CS. Shivering can be caused by cytokine production after surgery or a normal thermoregulatory adaptation to cerebral hypothermia (Sadeh et al., 2020). Shivering can disrupt monitoring, increase lactic acidosis and oxygen demand, and generate carbon dioxide (Faiz et al., 2013; Ghasemi et al., 2018; Miao et al., 2018). To prevent shivering, pharmacologic drugs, including magnesium sulfate (MS), opioids, α2-agonists, NMDA receptor antagonists, and serotonin 5-HT3 receptor antagonists have been studied (Lema et al., 2017; Liu et al., 2018; Sachidananda et al., 2018). Non-pharmacological therapies such as sheets, radiant warmth, and heated air warmers have also reduced shivering during the intraoperative and perioperative periods (Kiran and Sangineni, 2019). However, there is still a need for alternative therapies that are both effective and safe. Pethidine, considered the gold-standard drug for post-SA shivering, is not recommended for nursing mothers, making it ethically and legally problematic (Noaman et al., 2019). Therefore, finding a reliable and potent anti-shivering drug for pregnant women undergoing CS is crucial to replace pethidine.

Methodology

Between February 2021 and December 2022, a double-blind clinical trial was conducted at a tertiary care hospital in Lahore, Pakistan. The purpose of the trial was to evaluate the safety and effectiveness of tramadol, a low dose of ketamine, and a standard saline solution on post-spinal anesthesia shaking in term pregnant women aged 18-40 who were suitable for Cesarean section under spinal anesthesia, according to the American Society of Anesthesiologists (ASA) II categorization.

Information was gathered from all patients who had given informed consent, including their demographics, medical histories, and medications. The trial excluded pregnant women who had limitations or allergies to the study medications, a history of cardiovascular illness, mental illness, high blood pressure, fetal distress, early cord prolapse, a temperature greater than 38°C, a history of

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substance misuse, the necessity for a transfusion or any exceptional intraoperative or postoperative hemorrhage, the use of other medications that alter thermoregulation, failure of spinal anesthesia, or the need to switch to general anesthesia.

After inserting an 18 gauge IV cannula, 10mL/kg of ringer lactate solution was administered for 15 minutes. Standard monitoring was done for all patients, including an electrocardiogram (ECG), pulse rate, non-invasive measurements of blood pressure (BP), and saturation of oxygen (SPO2).

Spinal anesthesia was performed sitting using a 25-caliber Quincke spinal needle and 12.5 milligrams of bupivacaine at the L3-L4 or L4-L5 levels. The quality of the spinal anesthesia block was evaluated using the Bromage scale and Pinprick assessment. The intended sensory block was T4-T6, while 3 was considered appropriate for the motor system block and Bromage scale. The patients were randomly divided into three groups: tramadol 0.5 mg/kg (T), a low dose of ketamine 0.2 mg/kg (K), and placebo with normal saline (P). No premedication or active warning was given to the patients. The research medications were prepared in 5 mL labeled syringes by an anesthesiologist who was not involved in the study process, and an authorized anesthesiologist administered the drugs as an IV bolus shortly after verifying spinal anesthesia.

The intensity of shivering was monitored every 5 minutes throughout the operation and for 45 minutes afterward. Shivering severity was graded as follows: grade 0 - no shivering, grade I - slight shivering, grade II - moderate shivering, and grade III - severe shivering. After clipping the umbilical cord, pethidine 25 milligrams IV was administered to treat refractory shivering. If the HR was below fifty bpm, atropine 0.5 milligrams IV was administered. If the blood pressure decreased below 20% from the reference value or the systolic blood pressure was under 100 mmHg, ephedrine 5 mg IV was administered. If the individual reported vomiting and nausea, metoclopramide 10 mg IV was administered. During the trial, any negative drug response and hemodynamic variables were recorded.

The data was analyzed using SPSS software version 21. One-way analysis of variance (ANOVA) was used to evaluate continuous data variables with normal distributions and repeated-measures ANOVA was used to analyze temperature measurements. The Mann-Whitney U and chi-square tests were used to compare non-parametric information regarding shivering severity among groups. A P-value of < 0.05 was considered statistically significant.

Results

The socio-demographic statistics of the groups were evaluated and presented in Table 1. There were no statistically significant differences in baseline characteristics among the three groups. Additional demographic details of the patients are shown in the following table. Shivering was observed in 33 (55%), 12 (20%), and 41 (68.33%) patients in the K, T, and P groups, respectively. The difference in shivering severity across the three groups was significant (P = 0.0001) (refer to Table 2, Figure 1). Only 5 (8.3%) of the participants in the placebo group experienced grade 4 shivering, while none in the treatment groups did. Grade 3 shivering was observed in 7 (11.66%), 2 (3.3%), and 16 (10%) individuals in the K, T, and P groups, respectively. Table 3 displays the frequency of Adverse Drug Reaction (ADR) incidence.

Figure 1: Frequency of Shivering between the groups

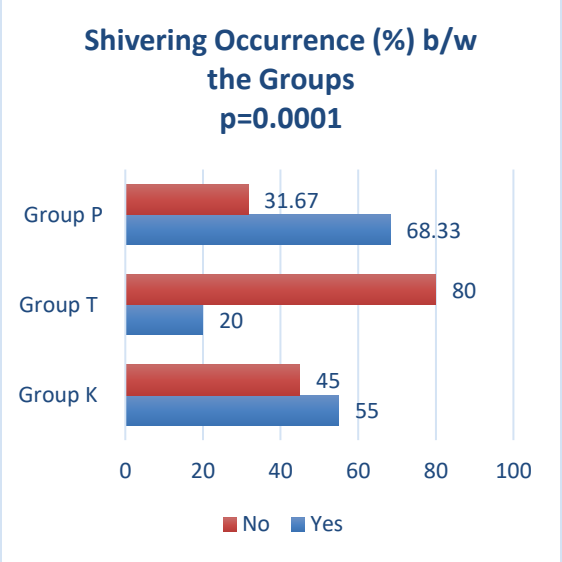

Table 1: Demographic details of patients

Variables	Group K (N = 60)	Group T (N = 60)	Group P (N = 60)	P-Value
ASA class				
I	45 (75)	43 (71.66)	47 (78.33)	**0.751**
II	15 (25)	17 (28.34)	13 (21.67)	
Age (y)	28.79 ± 4.55	28.19 ± 5.65	28.39 ± 4.86	0.855
Temperature (°C)	37.01± 0.24	37.05 ± 0.27	37.03 ± 0.75	0.554
Operating room temperature (°C)	22.29 ± 0.73	22.89 ± 0.93	22.49 ± 0.43	0.451
Duration of surgery (min)	53.4 ± 7.11	53.24 ± 5.11	53.44 ± 6.11	0.541
BMI (kg/m 2)	28.74 ± 4.52	28.44 ± 4.92	28.24 ± 4.22	0.235
Block sensory level				
2	11(19.34)	12(20)	10(16.67)	**0.454**
3	49(81.66)	48(80)	50(83.33)	

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Table 2: Assessment of Shivering Occurrence and Severity among Experimental Group

Parameters	Group K (N = 60)	Group T (N = 60)	Group P(N = 60)	p-value
Shivering (%)				
Yes	33 (55)	12 (20)	41 (68.33)	0.0001
No	27 (45)	48 (80)	19 (31.67)	
Severity of shivering (%)				
Grade I	15 (25)	6(10)	13(21.6)	0.0001
Grade II	11(18.33)	4(6.6)	17(28.3)	
Grade III	7(11.66)	2(3.3)	6(10)	
Grade IV	-	-	5(8.3)	

Table 3: The Prevalence of Adverse Events in Three Study Groups

Side Effects	Group K	Group T	Group P	p-value
Nausea &vomiting	12 (20)	31(51.66)	26(43.33)	0.0001
Hypotension	4(6.6)	14(23.33)	9(15)	0.001
Bradycardia	0 (0)	7(11.66)	4(6.6)	0.003
Hallucination	6(10)	0 (0)	0 (0)	0.0001
Nystagmus	5(8.33)	0 (0)	0 (0)	0.0001
Headache	3(5)	6(10)	2(3.3)	0.047

Discussion

In this study, the prevalence of shivering was 63.5%, higher than the rates found in previous studies. This could be due to differences in the operating room environment and patient demographics (Chowdhury et al., 2018). The research has shown that various medications can reduce post-spinal anesthesia shivering in different ways and degrees. Tramadol, a centrally-acting analgesic, is one such medication. Its anti-shivering properties are due to its ability to block the absorption of noradrenaline and serotonin in the spinal cord and to increase the production of hydroxyl-tryptamine, which is involved in the human temperature control center (Ejiro et al., 2014; Imani et al., 2011; Memarian et al., 2018). Among the medications studied, IV tramadol was the most effective. It is worth noting that the majority of the procedures in this study were performed by obstetric fellows under the guidance of attendings, resulting in a longer mean surgical length (54.61 ±5.46) compared to other studies, such as the Gemal survey (45.5 ±7.2) (Yousef and Elsayed, 2015). Similar to the findings in Gemal's trial, 23% of the tramadol group in this study reported shivering, while the proportion was 20% in the present study. However, only 7.16% of Gemal's patients in the tramadol group shivered, and none had severe grades (Ejiro et al., 2014). Talakoub, Noori Meshkati, and Seyam conducted two experiments that yielded similar encouraging findings. However, Ilyas et al. revealed different results, indicating the advantage of low-dose ketamine over IV tramadol. In this study, 0.02 mg/kg Intravenous ketamine significantly decreased the frequency and severity of shivering compared to placebo. Ketamine, an NMDA receptor antagonist, resets the thermoregulation system by altering serotoninergic and noradrenergic nerves. In addition to its anti-shivering effects, intravenous ketamine has other benefits, such as maintaining hemodynamic balance and providing pain relief after surgery (Imani et al., 2014; Imani and Varrassi, 2019).

Our study found that 55% of individuals in the ketamine group experienced shivering, which was significantly higher compared to Honarmand and Safavi's investigations (23.3%), Sagir et al.'s study (0%), and Jaafarpour et al.'s research (17.4%).

In a separate trial, Lema et al. discovered that ketamine 0.2 mg/kg was more effective than tramadol 0.5 mg/kg as an anti-shivering drug in CS under SA.

Kumar et al.'s study showed that the rate of shivering in the ketamine group was 33%, which was lower than ours. The difference might be due to the higher drug dosage (0.5 mg/kg vs. 0.2 mg/kg) used in Kumar et al.'s study.

In our research, the tramadol group experienced 20% shivering, with only 3.3% experiencing grade 3 shivering, while the ketamine group experienced 55%, with 11.66% experiencing grade 3 shivering. Therefore, studies without assessing the degrees of shivering may not be relevant. Additionally, the frequency of shivering in the placebo group is crucial when assessing a drug's anti-shivering capabilities.

There is a significant disparity between the outcomes of different investigations due to disparities in methodology, the investigated population, operating room settings, genealogy, fluid preheating, drug room temperature, and the extent of sensory block. Furthermore, patients were not scored with comparable precision in various investigations, so lesser degrees of shivering (0 and 1) may have gone undetected.

Finally, it has been demonstrated that the degree of shivering in pregnant women is highly connected to their level of anxiousness before surgery. (Wódarski et al., 2020). The incidence of perioperative drug-induced adverse reactions (DAR), such as nausea, vomiting, hallucination, and nystagmus, varied significantly among the three study groups in this research. We observed that the trial medications were significantly more effective than the placebo. However, the high incidence of shivering highlighted the need for appropriate management. Therefore, administering a good prophylactic medication based on patients' circumstances, such as their medical history, is highly recommended.

The study provided useful insights on preventing shivering during CS under SA. However, it had a few limitations. Firstly, it was conducted in a single center and did not

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include the private sector. Secondly, the temperature of the room and fluids could not be regulated accurately.

Conclusion

The study found that tramadol is the most effective medication for managing shivering, followed by a lower dosage of ketamine. Shivering was high in the placebo group, indicating that preventive treatment for shivering in CS under SA is necessary.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.
Ethics approval and consent to participate.
Approved by the department concerned.
Consent for publication
Approved
Funding
Not applicable

Conflict of interest

The authors declared the absence of conflict of interest.

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