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ORIGINAL ARTICLE

Randomized Double Blind Comparison of Prophylactic Tramadol and Tramadol Plus Ketamine for Prevention of Shivering after Spinal Anesthesia in Lower Segment Caesarian Section

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ABSTRACT

Objective: To assess the effectiveness of prophylactic intravenous tramadol alone versus a combination of tramadol and ketamine in preventing shivering during spinal anesthesia for lower segment caesarean section.

Methods: This double-blind randomized controlled trial was conducted at Ziauddin Hospital, North Nazimabad, Karachi, Pakistan from August 2023 to October 2023. Pregnant women aged between 18 to 40 years meeting American Society of Anesthesiologist physical status I and II admitted in hospital for lower segment caesarian section were enrolled. One group received an injection tramadol 0.5mg/kg whereas the other group received an injection of tramadol 0.25mg/Kg plus an injection ketamine 0.25 mg/Kg. The primary outcomes were incidence of shivering and severity of shivering. Time to shiver and complications were secondary outcomes.

Results: Of total 190 patients, the mean age was 25.95 ±3.63 years. Shivering was reported in 96 (50.5%) patients. The incidence of shivering was found significantly lower in tramadol plus ketamine group as compared to tramadol group i.e., 18 (18.7%) vs. 78 (81.3%) (p-value <0.001). Severity of shivering was found significantly lower in tramadol plus ketamine group as compared to tramadol group (p-value <0.001). Mean duration of shivering found significantly lower in tramadol plus ketamine group as compared to tramadol group i.e., 4.78 ±0.73 minutes vs. 8.46 ±1.02 minutes (p-value <0.001) respectively.

Conclusion: The incidence of shivering was significantly lower in the group receiving the combination therapy compared to those receiving tramadol alone. Notably, the severity and duration of shivering were also markedly reduced in the tramadol plus ketamine group.

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

Clinical Trial Registry#: NCT06134895

INTRODUCTION

Shivering after anesthesia, whether general or regional, is a common complication.[1] Studies have reported the incidence of shivering perioperatively at 40-78% while postoperatively at 20-56%.[1-3] Shivering, a prevalent consequence of spinal anesthesia, not only impair patient comfort but also holds potential physiological implications, which could affect the well-being of both the mother and the fetus.[4-7] Shivering during spinal anesthesia is multifactorial, involving a complex interplay of neurophysiological mechanisms triggered by alterations in temperature regulation.[8,9]

Intravenous tramadol, an opioid analgesic with central antineurotransmitter effects, has demonstrated efficacy in preventing shivering. However, concerns regarding its dose-dependent side effects, including nausea, vomiting, and opioid-related respiratory depression, necessitate additional exploration. Ketamine, an N-methyl-D-aspartate receptor antagonist with analgesic and neuromodulatory properties, has emerged as a promising alternative, exhibiting potent anti-shivering effects with a favorable side effect profile.[10]

The rationale for this study is rooted in the multifaceted nature of shivering, involving complex neurophysiological pathways. Tramadol, a centrally acting analgesic, has shown promise in mitigating shivering, but its effectiveness may vary. Ketamine, known for its analgesic and anesthetic properties, operates through

different neuroreceptor systems. Combining these two agents may offer synergistic effect, targeting various pathways involved in shivering induction. These combination might allow for a reduction in the dose of tramadol, potentially minimizing side effects such as nausea and vomiting, common concerns with its use.

METHODS

This double-blind phase IV randomized controlled trial was conducted at the Department of Anesthesiology, Ziauddin Hospital, North Nazimabad, Karachi, Pakistan, from August to October 2023. Prior to the initiation of the study, ethical approval was obtained from the Ethics Committee of Ziauddin University (ERC #: 7240623MAANE). The trial was registered in NCT06134895. Moreover, patients provided informed consent after receiving detailed explanations of the potential risks and benefits associated with the study.

Pregnant women aged 18 to 40 years, meeting American Society of Anesthesiologists (ASA) physical status I and II, who were admitted to the hospital for lower segment caesarean section, were included in the study. Women with hypo- or hyperthyroidism, a known history of cardiopulmonary disease, pre-eclampsia, eclampsia, an initial body temperature of 38.0°C or 36.0°C as assessed by a thermometer, or a known history of alcohol or substance abuse (such as hashish/marijuana), as well as those receiving like Atenolol, Acyclovir, or medications (antipyretic or antipyretic) likely to alter thermore-gulation, were excluded from the study.

By using OpenEPI sample size calculator taking incidence of shivering in tramadol plus ketamine group 15%,[11] level of confidence 95%, 5% margin of error. The estimated sample size was 196. However, 190 patients were enrolled. i.e., 95 in each group. All patients were included via non-probability consecutive sampling. A flow diagram showing the recruitment of patients is shown in Figure 1.

Upon entering the operating theater, all patients underwent venous cannulation. Intravenous (IV) fluids, preheated to 37°C in a warmed cabinet, were administered without in-line warming. Lactated Ringer's solution, adjusted to 37°C, was administered intravenously at a rate of 10 ml/kg/hr for a duration of 30 minutes prior to the administration of spinal anesthesia. Conventional non-invasive monitors were employed to observe and record heart rate, mean arterial pressure, and peripheral oxygen saturation prior to intrathecal injection, and thereafter at intervals of 5, 10, 15, 20, 25, and 30 minutes. Axillary body temperature was recorded using an axillary thermometer before intrathecal injection and at 15-minute intervals throughout the perioperative period. Subarachnoid anesthesia was administered at either the L3/L4 or L4/L5 interspaces. Hyperbaric Bupivacaine, with a concentration of 5 mg/ml and a dosage ranging

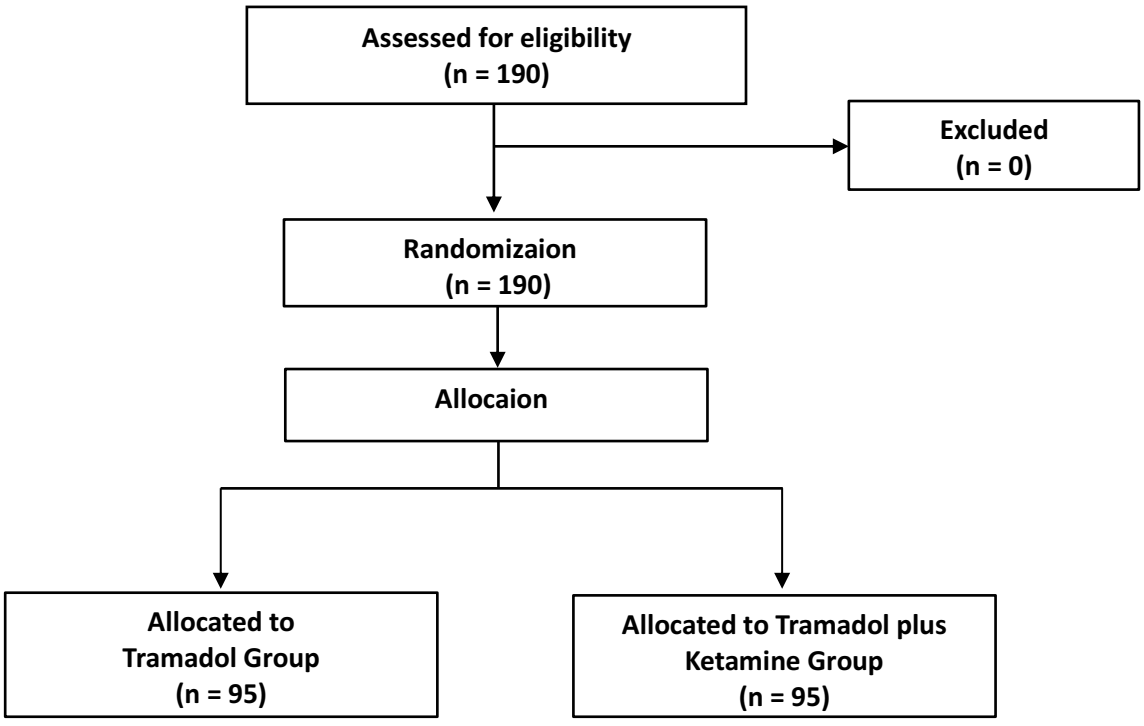

Figure 1: Flow diagram in accordance with CONSORT guidelines

from 10 to 12 mg, was administered utilizing a spinal needle with a gauge size of 25 and a Pencil Point design. Patients were randomly assigned to one of two groups using the sealed opaque envelope method. One group received a tramadol injection at a dosage of 0.5 mg/kg, while the other group received a combination injection of tramadol at a dosage of 0.25 mg/kg and ketamine at a dosage of 0.25 mg/kg.

Immediately following the intrathecal injection, all medications were administered as an intravenous bolus. The treatment substances were provided in coded syringes by an anesthesiologist. Both study participants and care providers were blinded to the drug, which was to be administered.

The primary outcomes were the incidence of shivering and the severity of shivering. Time to shiver and complications were secondary outcomes.

Shivering was assessed using a validated scale developed by Tsai and Chu,[12] comprising four categories. "Grade 0" denoted the absence of shivering, "Grade I" indicated piloerection or peripheral vasoconstriction without visible shivering, "Grade II" signified visible muscular twitching in a single muscle, "Grade III" indicated visible muscular twitching in multiple muscle groups but not generalized, and "Grade IV" represented shivering involving the entire body. Efficacy was defined as achieving shivering grades 0 to 1.

This data, along with demographic factors including age, gender, ASA status, length of surgical procedure, height, weight, body mass index (BMI), and comorbidities such as diabetes mellitus and hypertension, was recorded in a standardized form.

Data entry and statistical analysis were done using the Statistical Package for the Social Sciences (SPSS) version 24. Mean and standard deviation were calculated for all the quantitative variables like age, weight, height, BMI, and duration of surgery. Relevant description statistics, percentages and frequencies were calculated for all the qualitative variables such as gender, efficacy, ASA status, and comorbidities like diabetes mellitus and hypertension. The mean difference of quantitative variables between groups was explored using the independent t-test. The Chi-square test was applied to compare the efficacy of the tramadol group and tramadol plus ketamine group. The p-value ≤0.05 was taken as significant.

RESULTS

Of a total of 190 patients, the mean age, weight, height, and BMI were 25.95 ±3.63 years, 72.87 ±9.65 kg, 1.52 ±0.03 m, and 31.65 ±3.91 kg/m^2 respectively. There were 190 (100%) patients who had ASA grade II, and none had ASA grade I. Most patients had a duration of surgery ≤85 minutes, i.e., 125 (65.8%). Comorbidities like hypertension and diabetes mellitus were noted in 20 (10.5%) and 12 (6.3%) patients, respectively. Between-group comparison showed no significant mean differences with age (p-value 0.796), weight (p-value 0.899), height (p-value 0.098), BMI (p-value 0.695), and duration of surgery (p-value 0.460). Complications were observed significantly lower in the tramadol plus ketamine group 3 (23.1%) as compared to the tramadol group 10 (76.9%) (p-value 0.044) (Table 1).

Among 190 patients, shivering was reported in 96 (50.5%) patients. The incidence of shivering was found to be significantly lower in the tramadol plus ketamine group as compared to the tramadol group, i.e., 18 (18.7) vs. 78 (81.3) (p-value <0.001). Grade II/III severity of shivering was found to be significantly lower in the tramadol plus ketamine group as compared to the tramadol group, i.e., 10 (13.7%) vs. 63 (86.3%) (p-value <0.001) (Table 2).

The overall mean duration of shivering was 7.77 ±1.7 minutes. The mean duration of shivering was found to be significantly lower in the tramadol plus ketamine group as compared to the tramadol group, i.e., 4.78 ±0.73 minutes vs. 8.46 ±1.02 minutes (p-value <0.001) respectively (Table 3).

DISCUSSION

The present study aimed to assess the effectiveness of prophylactic intravenous tramadol alone versus a combination of tramadol and ketamine in preventing shivering during lower-segment caesarean section under spinal anesthesia. The results of this double-blind, phase IV randomized controlled trial suggest that the combination of tramadol and ketamine was more effective in reducing both the incidence and severity of shivering than tramadol alone.

Lower segment caesarean section performed under spinal anesthesia is a commonly practiced and established surgical technique for obstetric procedures.[13-17] Various pharmacological approaches have been investigated to proactively manage its adverse effects. However, uncertainties persist regarding the optimal dosage, side effect profile, and the necessity for supplementary agents to augment its effectiveness.[18-26] In recent years, numerous studies have examined the efficacy of ketamine in preventing post-anesthesia shivering. Ketamine, an affordable and widely accessible general anesthetic agent, induces

Table 1: Comparison of baseline and clinical characteristics of patients with groups (n=190)

Variables	Total	Group		p-value
		Tramadol (n=95)	Tramadol plus Ketamine (n=95)	
Age (years)	25.95 ±3.63	25.88 ±4.04	26.02 ±3.22	0.796~
≤25	89	43 (48.3)	46 (51.7)	0.663^
>25	101	52 (51.5)	49 (48.5)	
Weight (kg)	72.87 ±9.65	72.96 ±11.15	72.78 ±7.93	0.899~
Height (m)	1.52 ±0.03	1.52 ±0.03	1.51 ±0.02	0.098~
BMI (kg/m^2)	31.65 ±3.91	31.54 ±4.56	31.76 ±3.14	0.695~
≤30	83	45 (54.2)	38 (45.8)	0.306^
>30	107	50 (46.7)	57 (53.3)	
ASA				
I	0 (0)	0 (0)	0 (0)	-
II	190	95 (100)	95 (100)	
Duration of Surgery (minutes)	83.51 ±13.39	84.23 ±12.94	82.79 ±13.87	0.460~
≤85	125	60 (48.0)	65 (52.0)	0.445^
>85	65	35 (53.8)	30 (46.2)	
Comorbidities				
Diabetes Mellitus	12	5 (41.7)	7 (58.3)	0.551^
Hypertension	20	9 (45.0)	11 (55.0)	0.999^
Complications$				
Yes	13	10 (76.9)	3 (23.1)	0.044^*
No	177	85 (48.0)	92 (52.0)	

$Complications included nausea, vomiting and headache, ASA: American society of anesthesiologists
-Quantitative variables described by mean± standard deviation, Categorical variables described by frequencies (percentages)
*p-value ≤ 0.05 (~Independent t-test and ^Chi-Square test)

Table 2: Association of incidence and severity of shivering with groups (n=190)

Variables	Total	Group		p-value
		Tramadol (n=95)	Tramadol plus Ketamine (n=95)	
Shivering				
Yes	96	78 (81.3)	18 (18.7)	<0.001*
No	94	17 (18.1)	77 (81.9)	
Severity of Shivering				
Grade 0	94	17 (18.1)	77 (81.9)	<0.001*
Grade I	23	15 (65.2)	8 (34.8)	
Grade II/ III	73	63 (86.3)	10 (13.7)	

*p- value ≤ 0.05 (Chi-Square test)

Table 3: Between-group comparison of duration of shivering among patients with shivering (n= 96)

Variables	Total	Group		p-value
		Tramadol (n=78) Mean ±SD	Tramadol plus Ketamine (n=18) Mean ±SD	
After Spinal Time of Shivering (minutes)	18.97 ±3.36	19.15 ±3.27	18.22 ±3.68	0.291
Duration of Shivering (minutes)	7.77 ±1.74	8.46 ±1.02	4.78 ±0.73	<0.001*

*p-value ≤ 0.05 (Independent t- test)

analgesia and amnesia, with or without loss of consciousness, by antagonizing the N-methyl-D-aspartate receptor in the brain.[27] Tramadol, a centrally acting analgesic with μ-opioid agonist properties, has demonstrated efficacy in preventing and treating shivering, with fewer adverse effects compared to other μ-opioid agonists.[28]

The findings of this study demonstrate a statistically significant difference in the occurrence of shivering between the two groups, favoring the tramadol plus ketamine group. This notion supports the hypothesis that the addition of ketamine to tramadol provides a synergistic effect in preventing shivering during spinal anesthesia for the lower- segment caesarean section. The mechanism behind this synergism could be related to the distinct pathways of action of tramadol and ketamine, affecting various neurotransmitter systems involved in thermoregulation. Furthermore, the study demonstrated that the severity of shivering was significantly lower in the tramadol plus ketamine group. This finding is of clinical importance, as reducing the severity of shivering contributes to patient comfort and may have implications for maternal and fetal outcomes.

Our findings are in accordance with and build upon previous research investigating the preventive use of tramadol for shivering during regional anesthesia. While tramadol alone has been extensively studied, the combination of tramadol and ketamine has received less attention in this context, and our study provides novel evidence supporting its efficacy. Abdelrahman *et al.* compared the efficacy of tramadol alone versus tramadol combined with ketamine, noting a reduction in shivering incidence in the tramadol and ketamine group compared to the tramadol-only group.[11] Witte *et al.* reported complete elimination of post-anesthetic shivering by administering tramadol at wound closure.[28] Another study found a significantly lower shivering incidence in patients receiving either ketamine or tramadol compared to those receiving saline.[29]

Interestingly, according to the current study findings, there was no significant difference in the time to shivering between the two groups. This suggests that while the combination therapy may not affect the onset of shivering, it exerts a more pronounced effect in mitigating its intensity once initiated.

The overall complication rate observed in both groups was comparable, emphasizing the safety profiles of the interventions. However, a notable difference was observed in the frequency of nausea, vomiting, and headache. The tramadol-only group exhibited a higher frequency of these adverse effects, underscoring the potential advantage of the tramadol and ketamine combination in minimizing unwanted side effects associated with tramadol alone.

Several limitations must be acknowledged in interpreting the results of this study. The sample size, although calculated for statistical power, may limit the generalizability of our findings. Additionally, the single-center nature of the study warrants caution in extrapolating the results to broader populations. This study's focus on pregnant women undergoing lower-segment caesarean section is particularly relevant due to the unique considerations in this population. The potential impact of shivering on maternal thermoregulation and the developing fetus necessitates a nuanced approach to prophylaxis. Understanding the comparative efficacy of tramadol alone versus the combination of tramadol and ketamine is crucial for refining evidence-based guidelines in obstetric anesthesia. Incorporating a validated shivering grading scale enhances the precision of our outcomes assessment, providing a comprehensive understanding of the interventions' effects. Moreover, the inclusion of secondary outcomes such as time to shivering and complications broadens the scope of our investigation, offering insights into both the temporal aspects and safety profiles of the interventions. The demonstrated superiority of the tramadol and ketamine combination in preventing shivering suggests a potential modifica-

tion in clinical practice for patients undergoing lower-segment caesarean section under spinal anesthesia. Clinicians may consider this combination a prophylactic strategy to enhance patient comfort and improve perioperative outcomes. Furthermore, future research should also include sedation scores in the study.

CONCLUSION

The incidence of shivering was significantly lower in the group receiving the combination therapy compared to those receiving tramadol alone. Notably, the tramadol plus ketamine group exhibited a marked reduction in postoperative complications and a substantial decrease in the severity of shivering compared to the tramadol-only group. The duration of shivering was also notably shorter in the combined intervention group. These outcomes are of clinical significance, as mitigating the severity of shivering is conducive to patient comfort and may have implications for maternal and fetal well-being during the critical perioperative period.

ETHICAL APPROVAL: Ethical approval was obtained from the Ethical Committee of Ziauddin University prior to the commencement of the study (ERC #: 7240623MAANE, dated: 15th August, 2023).

AUTHORS' CONTRIBUTIONS: MA, ZM, HAM: The conceptualization and design of the study. MA, SS, HAM: Data collection, data analysis and interpretation. MA, RK: Drafting the article. MA, HAM, MH: Critical revision for significant intellectual contributions. All authors have approved the final version of the manuscript to be published.

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