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Compare The Efficacy Of Tramadol Alone With Combination Of Low Dose Ketamine & Tramadol In The Prevention Of Shivering

Ikram Ullah Khan [1], Tooba Mughal [2], Pavan Kumar [3], Dr Nadia Naeem[4], Asia Firdous[5], Dr Ali Nawaz Bijarani[6], Ibrahim Gulraiz[7],

[1]Consultant Anesthesia Department of Anesthesia Cardiac Family Fauji foundation Hospital Peshawar

[2]Consultant Anesthesia Department of Anesthesia the Indus Hospital Karachi

[3]Assistant Professor Department of Anaesthesiology Al Tibri Medical College & Hospital Isra University Karachi Campus

[4]Assistant Professor Department of Pharmacology Jinnah Sindh Medical University (JSMU) Karachi

[5]Associate Professor of Pharmacology Gurki Trust Teaching Hospital/ Lahore Medical and Dental College Lahore

[6]Assistant Professor Department of Pharmacology Jinnah Sindh Medical University (JSMU) Karachi

[7]Department of Anesthesia, Fauji Foundation Hospital, Rawalpindi

***Corresponding Author**

Ikram Ullah Khan

Consultant Anesthesia Department of Anesthesia Cardiac Family Fauji foundation Hospital Peshawar

Email ID : ikramsmc078@gmail.com

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ABSTRACT

Background: Post spinal anesthesia shivering (PSAS) is a common and distressing side effect associated with increased metabolic demand, cardiovascular stress and patient discomfort. Improvement of perioperative outcomes requires effective prevention strategies.

Objective:The objective was to determine the efficacy of tramadol alone versus a combination of tramadol with low dose ketamine in the prevention of shivering during spinal anesthesia.

Materials and Methods: This randomized controlled trial was conducted at Cardiac Family Fauji foundation Hospital Peshawar from January to June 2024 over a period of six months. Eight hundred and ninety two patients of ASA physical status I or II, between the ages of 18 and 65 years, scheduled for elective surgery with spinal anaesthesia were enrolled. Participants were randomly divided into two groups: Group A was given intravenous tramadol (1 mg/kg) and Group B was given intravenous tramadol (1 mg/kg) plus low dose ketamine (0.25 mg/kg). The incidence of shivering was the main outcome of the study. Time to onset of shivering and time from first dose of active drug to time of shivering onset or recovery were secondary endpoints. Analysis of data included using including chi-square tests for categorical variables, and independent t- tests for continuous variables.

Results: The tramadol plus ketamine group showed a significantly lower incidence of shivering at 23.3%, compared to 50.9% in the tramadol-alone group. This difference was highly statistically significant, with a p-value less than 0.001. Additionally, the onset of shivering was delayed in the combination group, occurring at an average of 24.83 ± 4.88 minutes compared to 20.04 ± 5.08 minutes in the tramadol group, which was also statistically significant (p-value less than 0.001). The duration of shivering was markedly reduced in the tramadol plus ketamine group, averaging 4.89 ± 2.08 minutes, compared to 9.83 ± 2.98 minutes in the tramadol-alone group, with a p-value less than 0.001. These findings remained consistent across all analyzed subgroups, including age, gender, weight, and ASA physical status.

Conclusion:The addition of ketamine to tramadol combines prophylactic efficacy through reduction in incidence, delay in

onset and minimization of duration of PSAS. The combination of valproate and propranolol has been demonstrated to be safe and effective for shivering management under spinal anesthesia..

Keywords: *Shivering, spinal anesthesia, tramadol, ketamine, randomized controlled trial.*

1. INTRODUCTION

Spinal anesthesia is often complicated by shivering, involuntary muscle contractions, which are frequent and difficult to manage. Since it leads to elevated oxygen consumption, cardiac output and metabolic demand, it will exacerbate postoperative recovery and causes patient discomfort [1,2]. In addition to its physiological impact, shivering will also interfere with pacemaker monitors, electrocardiograms and pulse oximeters, thus underscoring a need for effective preventive strategies in addition to the physiological impact of shivering [3].

The most studied among the pharmacological interventions is tramadol due to its antishivering properties. This modulates thermoregulation by μ-opioid receptor agonism along with serotonin and norepinephrine reuptake inhibition [4,5]. An effective agent like that, for example, is ketamine, which is an NMDA receptor antagonist and prevents the transmission of cold signals to thermoregulatory centers. Ketamine not only has antishivering effects, but also sedates and provides analgesia and is a valuable drug in perioperative management [6,7].

A highly effective shivering prevention strategy is the combination of tramadol and low dose ketamine. This method advantages from the dissimilar mechanisms of action of the two drugs, thereby, maximizing their benefits and minimizing side effects. Multidisciplinary evidence proves that these two act synergistically and decreases occurrence and magnitude of shivering more than those that are given alone. According to Lema et al., [1] prophylactic use of tramadol and ketamine decreased incidence and delayed the incidence of high grade shivering. Jouryabi et al. [9] also found that the combination decreased associated shivering complications such as nausea and sedation. These findings were further supported by research in cesarean section patients by Azam et al. [10] which included the enhanced thermoregulatory effects of the combination therapy, particularly in high risk populations.

This combination is reinforced by meta analyses and systematic reviews as to the clinical utility. However, we find that combining tramadol and ketamine leads to better perioperative outcomes than either drug administered alone with fewer perioperative complications. They also mentioned its safety profile [5] by stating its effectiveness on various patient populations.

However, shivering remains an ongoing problem in perioperative care, despite advances. However, the use of individual agents such as tramadol and ketamine have proven efficacious, and a synergistic effect can be achieved by combining these – shivering prevention is maximized, while side effects are minimized. Our aim in this study is to investigate the robustness of the efficacy of tramadol and low dose ketamine combination therapy as a method to prevent shivering under spinal anesthesia.

2. MATERIAL AND METHODS:

This study, conducted as a randomized controlled trial (RCT) at Cardiac Family Fauji foundation Hospital Peshawar, spanned from January to June 2024. Ethical clearance was obtained from the institutional review board, and all participants provided written informed consent prior to enrollment.

Eligible participants were patients aged 18–65 years, classified as American Society of Anesthesiologists (ASA) physical status I or II, and scheduled for elective surgeries under spinal anesthesia. Exclusion criteria included contraindications to spinal anesthesia, pre-existing conditions like hypothyroidism or fever, allergies to ketamine or tramadol, psychiatric illnesses, or the use of drugs affecting thermoregulation.

The sample size, calculated based on data from Sattar et al., involved 892 patients, with 446 in each group. The study aimed for a power of 80% and a significance level of 5%. In the referenced study, shivering was reduced in 38.9% of cases with the tramadol plus ketamine combination compared to 48.2% in the tramadol-alone group [12].

Participants were randomly divided into two groups using a computer-generated list. Group A received tramadol (1 mg/kg intravenously), while Group B was given tramadol (1 mg/kg) combined with low-dose ketamine (0.25 mg/kg intravenously). To ensure blinding, neither the participants nor the medical staff administering the treatments were aware of group allocations. Medications were prepared by an independent anesthetist.

Baseline demographics, including age, gender, weight, and ASA classification, were recorded. The primary outcome measured was shivering occurrence (Yes/No) within 30 minutes of spinal anesthesia. Secondary outcomes included the time to onset and the duration of shivering, recorded in minutes.

Data were analyzed using SPSS version 25. Categorical variables, such as shivering occurrence, were analyzed with chi-square tests, while continuous variables, including time to onset and duration of shivering, were evaluated using independent

t-tests. Statistical significance was defined as a p-value less than 0.05.

3. RESULTS:

The mean age of the participants was 41.49 ± 13.44 years, and the mean weight was 70.14 ± 9.99 kg. The average time to onset of shivering was 22.53 ± 5.55 minutes, while the mean duration of shivering was 7.51 ± 3.64 minutes. Data were complete for all 892 participants included in the analysis.

The occurrence of shivering was significantly lower in the **Tramadol + Ketamine group** compared to the **Tramadol Alone group**. Shivering was observed in 50.9% of patients in the Tramadol Alone group, while only 23.3% of patients in the Tramadol + Ketamine group experienced shivering. The difference between the two groups was statistically significant, with a p-value less than 0.001, indicating that this result is very unlikely to be due to chance (Table 1).

A subgroup analysis showed consistent reductions in shivering rates across all categories. Among participants aged 18–30 years, shivering occurred in 73 patients (55.3%) in the Tramadol Alone group compared to 25 patients (18.7%) in the Tramadol + Ketamine group. In the 31–45 years age group, shivering was observed in 70 patients (50.7%) in the Tramadol Alone group versus 33 patients (27.3%) in the Tramadol + Ketamine group. Similarly, in the 46–65 years group, 84 patients (47.7%) in the Tramadol Alone group experienced shivering compared to 46 patients (24.1%) in the Tramadol + Ketamine group. These differences were statistically significant, with all p-values less than 0.001. Gender-based analysis revealed similar trends, with shivering occurring in 119 male patients (55.3%) and 108 female patients (46.8%) in the Tramadol Alone group, compared to 61 male patients (27.2%) and 43 female patients (19.4%) in the Tramadol + Ketamine group. These gender-based differences were also statistically significant, with p-values less than 0.001.

A weight-based analysis showed that shivering was reduced across all weight categories in the Tramadol + Ketamine group. For participants weighing <60 kg, shivering occurred in 39 patients (52.7%) in the Tramadol Alone group and 16 patients (19.0%) in the Tramadol + Ketamine group. In the 60–80 kg weight category, shivering was observed in 157 patients (50.2%) in the Tramadol Alone group versus 70 patients (22.9%) in the Tramadol + Ketamine group. In the >80 kg weight group, 30 patients (51.7%) in the Tramadol Alone group experienced shivering compared to 17 patients (30.9%) in the Tramadol + Ketamine group. The differences in shivering rates across all weight categories were statistically significant, with p-values less than 0.001.

Analysis based on ASA physical status also revealed significant differences. Among ASA I patients, 103 patients (52.3%) in the Tramadol Alone group experienced shivering compared to 59 patients (25.7%) in the Tramadol + Ketamine group. Similarly, among ASA II patients, shivering occurred in 124 patients (49.8%) in the Tramadol Alone group compared to 45 patients (20.8%) in the Tramadol + Ketamine group. The differences across ASA categories were statistically significant, with p-values less than 0.001 (Table 2).

In terms of time to onset and duration of shivering, significant improvements were observed in the Tramadol + Ketamine group. The average time to onset of shivering was longer in the Tramadol + Ketamine group (24.83 ± 4.88 minutes) compared to the Tramadol Alone group (20.04 ± 5.08 minutes). This difference was statistically significant, with a p-value less than 0.001. Additionally, the duration of shivering was shorter in the Tramadol + Ketamine group (4.89 ± 2.08 minutes) compared to the Tramadol Alone group (9.83 ± 2.98 minutes). This reduction was also statistically significant, with a p-value less than 0.001 (Table 3).

Overall, the addition of ketamine to tramadol significantly reduced shivering occurrence, delayed its onset, and minimized its duration. These findings provide robust evidence supporting the clinical use of this combination therapy for managing shivering under spinal anesthesia.

Table 1: Comparation of shivering between the both groups

Group	No Shivering n (%)	Shivering Occurred n (%)	P value
Tramadol Alone	219 (49.1%)	227 (50.9%)	0.000
Tramadol + Ketamine	342 (76.7%)	104 (23.3%)	

Table 2: Comparison of Shivering Occurrence Across Age, Gender, Weight, and ASA Physical Status Between Tramadol Alone and Tramadol + Ketamine Groups

Variable	Subgroup	Group	No Shivering n (%)	Shivering Occurred, n (%)	Total n (%)	p-value
Age Group	18–30 years	Tramadol Alone	59 (44.7%)	73 (55.3%)	132	<0.001
		Tramadol + Ketamine	109 (81.3%)	25 (18.7%)	134	
	31–45 years	Tramadol Alone	68 (49.3%)	70 (50.7%)	138	<0.001
		Tramadol + Ketamine	88 (72.7%)	33 (27.3%)	121	
	46–65 years	Tramadol Alone	92 (52.3%)	84 (47.7%)	176	<0.001
		Tramadol + Ketamine	145 (75.9%)	46 (24.1%)	191	
Gender	Male	Tramadol Alone	96 (44.7%)	119 (55.3%)	215	<0.001
		Tramadol + Ketamine	163 (72.8%)	61 (27.2%)	224	
	Female	Tramadol Alone	123 (53.2%)	108 (46.8%)	231	<0.001
		Tramadol + Ketamine	179 (80.6%)	43 (19.4%)	222	
Weight Group	<60 kg	Tramadol Alone	35 (47.3%)	39 (52.7%)	74	<0.001
		Tramadol + Ketamine	68 (81.0%)	16 (19.0%)	84	
	60–80 kg	Tramadol Alone	156 (49.8%)	157 (50.2%)	313	<0.001
		Tramadol + Ketamine	236 (77.1%)	70 (22.9%)	306	
	>80 kg	Tramadol Alone	28 (48.3%)	30 (51.7%)	58	0.025
		Tramadol + Ketamine	38 (69.1%)	17 (30.9%)	55	
ASA Status	ASA I	Tramadol Alone	94 (47.7%)	103 (52.3%)	197	<0.001
		Tramadol + Ketamine	171 (74.3%)	59 (25.7%)	230	
	ASA II	Tramadol Alone	125 (50.2%)	124 (49.8%)	249	<0.001
		Tramadol + Ketamine	171 (79.2%)	45 (20.8%)	216	

Table 3: Comparison of Time to Onset of Shivering and Duration of Shivering Between Tramadol Alone and Tramadol + Ketamine Groups

Variable	Group	N	Mean ± SD	p-value
Time to Onset (Minutes)	Tramadol Alone	446	20.04 ± 5.08	<0.001
	Tramadol + Ketamine	446	24.83 ± 4.88	
Duration (Minutes)	Tramadol Alone	446	9.83 ± 2.98	<0.001
	Tramadol + Ketamine	446	4.89 ± 2.08	

4. DISCUSSION:

Post-spinal anesthesia shivering (PSAS) is a frequent and undesirable complication of regional anesthesia, associated with significant discomfort, increased metabolic demand, and potential cardiovascular stress [12,13]. Effective management strategies are essential to minimize these risks and improve patient outcomes. Our study findings strongly support the combination of tramadol and ketamine as a superior approach to managing PSAS, with significant reductions in the incidence, severity, and duration of shivering compared to tramadol alone. These results align with the growing body of literature on this topic.

Sattar et al. [12] demonstrated that adding low-dose ketamine (0.25 mg/kg) to tramadol reduced shivering incidence from 48.2% in the tramadol group to 38.9% in the combination group. This reduction highlights the potential synergy between tramadol and ketamine in modulating thermoregulation. Similarly, Naz et al. [13] observed a lower frequency of shivering (68.4% vs. 85.2%) and a delayed onset of shivering (33.1 ± 2.8 minutes vs. 24.01 ± 1.9 minutes) in patients receiving the combination therapy. These findings parallel our results, where the tramadol and ketamine group consistently outperformed tramadol alone across various patient subgroups.

The role of ketamine in reducing shivering severity and duration is further highlighted in studies like Arif et al. [14], which reported a significantly lower incidence of shivering (18.7% vs. 81.3%) and shorter shivering duration (4.78 ± 0.73 minutes vs. 8.46 ± 1.02 minutes) in the combination group compared to tramadol alone. Our findings, showing reduced severity and duration in the combination group, align closely with these observations.

Meta-analyses and broader reviews provide additional evidence for the effectiveness of ketamine. Fenta et al. [15] conducted a meta-analysis of 13 studies involving 1,532 patients, concluding that ketamine was comparable to tramadol in shivering prevention but had fewer adverse effects like nausea and bradycardia. However, ketamine was associated with a higher incidence of hallucinations, emphasizing the need for careful dosing to balance efficacy and safety.

The prophylactic use of tramadol and ketamine has been evaluated in diverse clinical contexts, including cesarean sections and orthopedic surgeries. Faraz et al. [16] demonstrated that tramadol and ketamine effectively reduced shivering incidence and intensity compared to placebo, with tramadol showing slightly higher efficacy. Similarly, Seyam et al. [17] reported a significant reduction in grade 3 shivering with ketamine and tramadol compared to placebo, highlighting their effectiveness in managing moderate-to-severe shivering.

Our findings also align with studies evaluating alternative agents. Ameta et al. [18] compared ketamine, tramadol, and dexmedetomidine for shivering prevention, concluding that dexmedetomidine was the most effective but often associated with hypotension. These limitations make tramadol and ketamine a more practical choice for patients where hemodynamic stability is a priority.

While most studies emphasize the efficacy of tramadol and ketamine, variations in study populations and methodologies highlight the need for tailored approaches. For example, Gemechu et al. [19] found that low-dose ketamine significantly reduced the incidence of shivering in orthopedic patients, supporting its use as a prophylactic agent. Goich et al. [20], in a scoping review, emphasized the comparable efficacy of ketamine and tramadol, recommending patient-specific strategies based on clinical context and drug side-effect profiles.

Our study contributes to this growing body of evidence by demonstrating that tramadol combined with ketamine effectively reduces the incidence, severity, and duration of shivering across diverse patient demographics, including varying ages, weights, and ASA statuses. This combination provides a synergistic mechanism: tramadol acts on the μ-opioid receptor and serotonin-norepinephrine pathways, while ketamine modulates NMDA receptors, enhancing thermoregulatory stability [12,14,15].

5. CONCLUSION:

The combination of tramadol and ketamine significantly reduces the incidence, severity, and duration of shivering compared to tramadol alone in patients undergoing spinal anesthesia. Our results demonstrate that this combination not only delays the onset of shivering but also provides superior overall control, with consistent efficacy across various patient subgroups, including age, gender, weight, and ASA status. These findings highlight the synergistic effect of tramadol and ketamine, offering an effective, safe, and practical approach to managing post-spinal anesthesia shivering, thereby improving patient comfort and perioperative outcomes

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