

ORIGINAL RESEARCH

ANESTHESIOLOGY

Addition of low dose ketamine to tramadol for prevention of post-anesthetic shivering: a comparative study

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Abstract

Background and objectives: Post-anesthetic shivering (PAS) is a common complication following general and regional anesthesia. It is important to identify centrally-acting analgesic drugs that can effectively prevent and treat shivering with fewer side effects other than opioid agonists. Our study compared the effect of addition of low dose ketamine to tramadol for the prevention of shivering under spinal anesthesia.

Methodology: This randomized controlled trial study was conducted for six months, from May 01, 2016 to October 10, 2016, at Department of Anesthesiology, Surgical ICU and Pain Management, Civil Hospital Karachi, Pakistan.

All patients with ages between 18 to 50 y, of both genders, American Society of Anesthesiologist physical status I and II, scheduled for inguinal hernia surgeries were included. The patients were randomly allocated to Group T (inj. tramadol 0.5 mg/kg) and Group KT (inj. ketamine 0.25 mg/kg plus Tramadol 0.25 mg/kg). Shivering was graded 1–5, and was labeled as positive if the grade was 2–5. Time to shivering was noted from the administration of spinal anesthesia to onset of shivering. Perioperative complications such as nausea, vomiting, hypotension or bradycardia, were recorded

Results: The study included 190 patients, with 95 in each group. Demographic characteristics, ASA classification, and perioperative vitals of both groups were comparable ($p > 0.05$). The frequency of shivering in patients of Group KT was lower as compared to Group T [65(68.4%) vs. 81(85.2%); ($p < 0.05$)] respectively. Group T had earlier onset of shivering than Group KT [24.01 \pm 1.9 min vs. 33.1 \pm 2.8 min; ($p < 0.05$) respectively. Perioperative complication such as nausea, vomiting, hypotension and bradycardia were also less in the Group KT.

Conclusion: The prophylactic use of low-dose ketamine plus tramadol for the prevention of shivering is better than tramadol alone under spinal anesthesia.

Abbreviations: PAS Post-anesthetic shivering; NMDA N-methyl-d-aspartate; bmi Body mass index

Key words: Intravenous; Tramadol; Ketamine; Shivering, Postoperative; Anaesthesia, Spinal

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1. Introduction

Post-anesthetic shivering (PAS) is a common complication following general and regional anesthesia.

Various studies report the incidence of PAS to be between 5% to 65% in patients recovering from general anesthesia and 40% to 60% in patients recovering from regional anesthesia.¹⁻³ Shivering, apart from causing

discomfort to the patient, increases oxygen demand, hampers patient monitoring, increases catecholamine levels subjecting the patient to a higher risk of cardiovascular complications and increases intracranial and intraocular pressures.^{4,5}

Various pharmacologic agents have been used for prophylaxis and treatment of PAS, including serotonin receptor antagonist like odanserton,³ the α_2 blockers like clonidine and dexmedetomidine,^{6,7} opioids like fentanyl, tramadol and meperidine,⁸ anticholinergics like physostigmine, NMDA receptor antagonists like ketamine.⁹ In the recent years, several studies have evaluated the efficacy of ketamine for prevention of PAS.

Ketamine is an inexpensive, widely available general anesthetic agent that produces analgesia and amnesia, with or without the loss of consciousness, by antagonizing the NMDA receptors in the brain.⁹ Tramadol, which is a centrally acting analgesic drug as μ -opioid agonist, has been found effective in the prevention and treatment of PAS with less side effects than other μ -opioid agonists.¹⁰

Reda S. Abdelrahman compared tramadol and tramadol plus ketamine and observed that decrease in shivering in tramadol plus ketamine group was significantly more than tramadol alone (15% vs. 30%).⁹ There are many studies conducted on individual roles of tramadol and ketamine in different doses for prevention of shivering but literature review reveals that the combination of ketamine and tramadol has not been studied for same purpose. The rationale of this study was to compare the anti-shivering efficacy of tramadol plus ketamine with that of tramadol alone for prevention of shivering under spinal anesthesia.

2. Methodology

After obtaining formal approval from Research Evaluation Unit of College of Physicians & Surgeons Pakistan, this trial was conducted in operating room complex of Dr. Ruth Pfau Civil Hospital, Karachi, Pakistan from May to October 2016. Written informed consent was taken from the included patients and explained about the potential risk and benefits of the study drug/s. Sampling was done with non-probability consecutive method. Sample size was calculated by using WHO calculator taking shivering in tramadol group to be 30% and shivering in tramadol plus ketamine group 15%, significance level 5%, and power 80%.⁹ Sample size (n) was found to be 190 patients (95 in each group). Patients undergoing inguinal hernia surgery, to 50 y of age and ASA status I or II were enrolled. Patients with unstable cardiac disease, other systemic diseases, and preoperative hypothermia or hyperthermia, were excluded.

Primary outcome of the study was to assess and compare the anti-shivering effect of low dose ketamine plus tramadol and tramadol alone. The secondary outcome was the frequency of nausea, vomiting, hypotension and bradycardia in each group.

Shivering was graded using a scale similar to that validated by Lema¹⁰ (e.g. 0 = no shivering; 1 = piloerection or peripheral vasoconstriction but no visible shivering; 2 = muscular activity in only one muscle group; 3 = muscular activity in more than one muscle group but not generalized; and 4 = shivering involving the whole body).

Nausea / vomiting was similarly graded as 0 = no nausea and vomiting; 1 = only nausea; 2 = nausea and vomiting once, and 3 = multiple episode.¹²

Time to shivering ($time_s - time_0$) means time from injection of local anesthetic in subarachnoid space ($time_0$) to time of onset of shivering ($time_s$).

Bradycardia means heart rate < 60 beats/min; hypotension means systolic blood pressure < 90 mmHg.

On arrival in the operating room (OR), NIBP, oxygen saturation and electrocardiogram were monitored and baseline values were recorded. Lactated ringer's solution was infused at 10 ml/kg/h over 15 min. Monitoring and recording of hemodynamic data continued every 5 min till discharge of the patient from recovery. OR temperature was set at 24° C as per institutional policy. Before intrathecal injection body temperature (T_0) was recorded with a mercury axillary thermometer. Another temperature reading was taken at the onset of shivering (T_1). Subarachnoid anesthesia was instituted at either L3/4 or L4/5 interspaces. Hyperbaric bupivacaine 5 mg/ml, 15 mg was injected using a 25G Quincke spinal needle. The patients were randomly allocated to Group KT and Group T by using sealed opaque envelop method. Just after intrathecal injection, all drugs were given as an intravenous bolus. Study drugs were prepared and diluted to a volume of 5 ml and were presented as coded syringes. All patients were under close observation by a blinded anesthesiologist for the incidence and intensity of shivering. Group KT received ketamine 0.25 mg/kg plus tramadol 0.25 mg/kg; whereas, Group T received tramadol 0.5 mg/kg.

Onset of shivering ($T_s - T_0$) recorded as time from spinal anesthesia (T_0) to onset of shivering (T_s). Shivering above Grade 2 was treated with rescue treatment in the form of intravenous pethidine 25 mg. Nausea and vomiting were also recorded and graded as 0–3, with grade zero being no vomiting. Grade 1–3 was taken as positive for vomiting.

Patients were monitored for shivering, nausea / vomiting, hypotension and bradycardia after intrathecal injection till 2 h postoperatively. This information along

Table 1: Socio-demographic and surgical characteristics. Data presented as n (%).

Parameter		Total (n = 190)	Group KT (n = 95)	Group T (n = 95)	p-value
Age (y)	35 and below	87 (45.8)	43 (45.2)	44 (46.3)	> 0.05
	More than 35	103 (54.2)	52 (54.7)	51 (53.7)	
Gender	Male	185 (97.4)	92 (96.8)	93 (97.9)	
	Female	5 (2.6)	3 (3.2)	2 (2.1)	
BMI(kg/m²)	30 and less	110 (57.9)	56 (58.9)	54 (56.8)	
	More than 30	80 (42.1)	39 (41.1)	41 (43.2)	
Comorbid	Hypertension	79 (41)	36 (37)	43 (45)	
	Diabetes Mellitus	72 (37.9)	36 (37.9)	36 (37.9)	
ASA	I	70 (36.8)	36 (37.9)	34 (35.8)	
	II	120 (63.2)	59 (62.10)	61 (64.2)	
Duration of surgery (min)		53.6 ± 5.44	54.2 ± 6.6	53.1 ± 4.1	

Table 2: Baseline vitals preoperatively. Data expressed Mean ± SD

Vitals	Total (n = 190)	Group KT (n = 95)	Group T (n = 95)	p-value
MAP (mm Hg)	75.2 ± 13.9	75.15 ± 13	74.24 ± 15	> 0.05
SpO ₂	98.7 ± 0.98	98.7 ± 0.99	98.7 ± 0.96	
Heart beats/min	82.01 ± 3.8	81.86 ± 3.9	82.16 ± 3.8	
Temperature °C	36.6 ± 0.1	36.67 ± 0.1	36.67 ± 0.1	

SpO₂; oxygen saturation; MAP - Mean arterial pressure

with demographics and comorbid conditions were noted in a proforma attached as annexure by the anesthesiologist who performed spinal anesthesia.

Statistical analysis: Data were analyzed with SPSS version 17. Normality of data was assessed with Kolmogorov–Smirnov test. Quantitative variables were compared using Student's t-test or Mann–Whitney U-test. Qualitative variables were compared with chi square and Fisher's exact test. Degree of association between independent and dependent variables was assessed by using odds ratio with 95% confidence interval. Variables with p-value of less than 0.05 were considered as significant.

3. Results

Socio-demographic characteristics are demonstrated in Table 1. Mean age of the patients was 36.46 ± 10.13 y. Majority of the patients in Group T and Group KT were >35 y of age, i.e. 51 (53.7%) and (54.7%) respectively. Patients under study were mostly males in Group T and KT i.e. 93 (97.9%) and 92 (96.8%) respectively. Mean BMI of patients was 29.96 ± 5.13 kg/m². Comorbidities of patients in both groups were also comparable, with 63.2% patient belonging to ASA class II. Mean duration

of surgery was 53.60 ± 5.44 min, with 53.1 ± 5.44 min and 54.2 ± 6.6 min in Group T and Group KT respectively.

There was no difference in recorded baseline hemodynamic data, e.g., mean arterial pressure, pulse rate and SpO₂. Preoperative axillary temperature was also comparable among the groups with p > 0.05. (Table 2) Mean temperature drop (T₁- T₀) at the time of shivering was found to be 1.23 ± 0.5° C. There was no significant difference between temperature drops in two groups. Table 3 explains the frequency distribution of shivering between both groups.

In Group T, 81(55.4%) patients experienced shivering as compared to 65 (44.5 %) in Group KT, showing effectiveness of the low dose ketamine plus tramadol for prevention of shivering (odds ratio [OR]: 2.6; 95% CI: 1.3-5.4; p = 0.006). There was significant difference in timings of onset of shivering in both groups. Patients in Group T had earlier onset of shivering as compared to Group KT with 23.9 ± 1.8 and 33.5 ± 2.3 min respectively.

Table 4 demonstrates comparison of safety profiles of both groups. A total of 10 (5.3%) patients experienced hypotension, out of which 8 (80%) were from Group T

Table 3: Comparison of effects of low dose ketamine plus tramadol and tramadol alone on shivering.

Parameter	Total (n = 190)	Group KT (n = 95)	Group T (n = 95)	p-value
Shivering [n (%)]	146 (76.8)	65 (68.4)	81(85.2)	0.006
Time to shivering (min) Mean \pm SD	28.1 \pm 5.2	33.5 \pm 2.3	23.9 \pm 1.8	0.003

Table 4: Comparison of Safety profiles of low dose ketamine plus tramadol and tramadol alone. Data given as n (%)

Parameter	Total (n = 190)	Group KT (n = 95)	Group T (n = 95)	p-value
Nausea & vomiting	13 (6.8)	3 (3.1)	10 (10.5)	0.041
Bradycardia	2 (1.1)	0 (0)	2 (2.1)	0.155
Hypotension	10(5.3)	2(2.1)	8(8.4)	0.05

(odds ratio [OR]: 4.25; 95% CI: 0.88–20.69; $p = 0.05$). Patients in Group KT experienced less nausea / vomiting as compared to Group T with 3 (23.1%) vs. 10 (76.9%) patients respectively (odds ratio [OR]: 3.6; 95% CI: 0.96-13.5; $p = 0.041$).

Bradycardia was noted in 2 (1.1%) patients, both were from Group T ($p = 0.155$).

4. Discussion

Combination of low dose ketamine and tramadol was compared with tramadol alone for prevention of shivering after spinal anesthesia in our study. Shivering was noted in 146 (76.8%) of the patients which is higher as compared to 40-60% in other studies.¹¹ A total of 44 (23%) of the patients remained shivering free, out of which 14 (14.7%) were in Group T and 30 (31.6%) belonged to Group KT. This shows that combination of low dose ketamine with tramadol is better in preventing post anesthesia shivering. Same trends were reported in a meta-analysis by Yang Zhou et al.¹³ Thangavelu et al. used intravenous ketamine in bolus doses followed by infusion in lower limb and abdominal surgeries under spinal anesthesia. They reported shivering in 13.9 % in ketamine group as compared to 54% in saline group which was lower than our study.¹⁴ Higher rates of shivering in our study could be because we did not and we didn't use fluid warmer intraoperative. Akram *et al.* compared ketamine and tramadol to control postoperative shivering and reported that ketamine controlled postoperative shivering better than tramadol.³

Intravenous opioids are known to cause nausea and vomiting. Incidence of nausea 10–20% and vomiting 3–9% are reported with intravenous tramadol which is a synthetic opioid in different studies.¹⁵ We reported nausea / vomiting in 13 (6.8%) patients out of which 10 (10.5%) belonged to Group T. In our study no significant

bradycardia was seen in any groups. However, hypotension was seen in 10 (5.3%) patients out of which 8 (8.4%) belonged to Group T. In a meta-analysis of randomized control trials to prevent post spinal shivering, patients who received tramadol experienced 2.2% hypotension.¹⁶ This is markedly lower than in our study where 8 (8.4%) patients experienced hypotension in Group T. Drugs which are used for prevention of shivering indirectly effect thermoregulatory system but drop in temperature was found to be same among groups.

Mean temperature drop from pre-spinal to onset of shivering was 1.2 ± 0.5 °C, but there was no significance difference among the groups, which is in accordance with a study in which graniseron, dexmedetomidine and tramadol were compared for prevention of shivering.^{17,18} This is because spinal anesthesia produces peripheral vasodilation, so there is core to periphery distribution of heat causing drop in temperature.

In our study, Group T had earlier onset of shivering with mean time 24.01 ± 1.9 min as compared to Group KT which is 33.1 ± 2.8 min. These results are different from a study by Lema in which onset to shivering was reported to be shorter in ketamine group as compared to tramadol group,¹⁰ which indirectly support that combination of ketamine and tramadol is better than ketamine or tramadol alone. In a study by Thalaguv, mean time of shivering after spinal was reported between 15 to 25 min which is in agreement with our study.¹⁴

Overall low dose ketamine plus tramadol is found to be more effective than tramadol alone to prevent shivering and causing fewer complications such as nausea / vomiting, hypotension and bradycardia.

5. Conclusion

The effect of prophylactic use of intravenous low dose ketamine plus tramadol for prevention of shivering was found better than that of tramadol alone under spinal anesthesia. Moreover, the incidence of nausea, vomiting, hypotension and bradycardia is also low with ketamine plus tramadol compared to tramadol alone.

7. Limitations

We took only ASA 1 & II patients with inguinal hernia surgery, with less exposure and minimal blood loss. This group of patients is associated with less shivering. Moreover, we did not use pre-warm fluids and we did not control theater temperature tightly which could have contributed towards such high percentages of Post-anesthetic shivering.

8. Acknowledgment

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9. Conflict of interest

None declared by the authors. No grant or funding was involved in the study.

10. Authors' contribution

SB: Conceived and designed the study, data collection, manuscript writing, acquisition analysis and interpretation of data, final revision.

AN: Supervision, critical revision for intellectual contents

VK: Final revision of article, accountable for accuracy and integrity of article.

SK, SJ: Revising article critically for intellectual contents

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PROFORMA USED FOR RECORDING THE DATA

Prophylactic intravenous low dose ketamine plus tramadol and tramadol alone to prevent post anesthetic shivering: A comparative study

PATIENTS DATA

Name: _____ CR# _____

Age: _____ Sex: Male Female

Weight: _____ kg Height: _____ meters

BMI: _____ kg/m² ASA Status I II

Duration of surgery: _____ min

T₀ = time of spinal _____ T_s = time of shivering _____

Axillary T₀ = Temperature pre-spinal _____ Axillary T₁ = Temperature at onset of shivering _____

Comorbids:

- DM
 HTN
 Group KT: 0.25mg/kg ketamine plus tramadol 0.25mg/kg
 Group T: Tramadol 0.5mg/kg

Shivering; yes / no

Nausea / vomiting; yes / no

Bradycardia; yes / no

Shivering

0 = no shivering; **1** = piloerection or peripheral vasoconstriction but no visible shivering; **2** = muscular activity in only one muscle group; **3** = muscular activity in more than one muscle group but not generalized; and **4** = shivering involving the whole body

Shivering grade 2 to 4 was taken as positive for shivering.

Nausea vomiting 0 = no nausea and vomiting, **1** = only nausea, **2** = nausea and vomiting once, **3** = nausea and vomiting multiple episode¹²

Grade 1-3 was taken as positive for vomiting.