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Randomised Comparative Study of Prophylactic Ketamine And Tramadol For Control Of Shivering Under Neuraxial Anaesthesia

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Abstract
Introduction: *Shivering is a common problem during neuraxial anaesthesia. Neuraxial anaesthesia impairs thermoregulatory control and up to a 56.7% incidence of shivering has been reported.*
Aim: *To evaluate the effectiveness of prophylactic use of intravenous ketamine and tramadol in control of shivering and to note any side-effects of the drugs used.*
Material and Methods: *Randomized double-blind study was conducted in 90 ASA grade I and II patients. Neuraxial block was performed with 0.5% bupivacaine heavy in all patients. The patients were randomly allocated into three groups of 30 each to receive saline as placebo (group C), ketamine 0.5 mg/kg (group K) and tramadol 0.5 mg/kg (group T). Temperature and hemodynamic parameters were recorded at every 5 min interval. Shivering was graded from 0 to 4.*
Statistical Analysis: *Data among groups was compared using one-way ANOVA. The incidence of shivering and side-effects were compared using the chi-square test.*
Results: *The incidence of grade 3 shivering showed a statistically significant difference (P=0.001) in group C as compared with Group T and Group K. No drug showed any statistically significant advantage over the other.*
Conclusion: *The prophylactic use of ketamine and tramadol were effective in preventing shivering during neuraxial anaesthesia.*
Keywords: *Ketamine, Tramadol, Neuraxial blockade, Shivering*

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I. Introduction

Shivering is defined as an involuntary, spontaneous and repetitive muscular activity. It is a common problem during spinal anesthesia due to vasodilation, which could facilitate rapid heat loss and core to peripheral redistribution of body heat, resulting in hypothermia that decreases the threshold for shivering.[1-4]

Around 50-60% of patients during surgeries under regional anesthesia experience shivering intraopreatively.[5,6] It is very unpleasant and physiologically stressful and may also cause complications, especially in the patients with coronary artery disease, because it leads to increase in oxygen consumption by 1-6%.[7,8] These complications can lead to cardiovascular and neurological deficits, as well as organ damage. Shivering if not treated, may adversely affect patient's outcome, leads to prolong recovery and prolong hospitalization.[9,10]

Various non pharmacologic techniques such as forced air warmers, blankets and increasing the operating room ambient temperature prevent shivering through maintenance of the core body temperature. However, these methods are expensive and cumbersome to use.[11] Different pharmacologic agents including opioids, NMDA receptor antagonists, magnesium sulphate, α2-agonists, cholinomimetics and biogenic amines have been used for prevention of post-spinal shivering. However, a "gold standard" drug treatment has not been defined.

Tramadol, a centrally acting analgesic drug with μ-opioid agonist, has shown to be effective in the prevention of post spinal shivering. It has modulatory effect on central monoaminergic pathways by inhibiting the neuronal uptake of noradrenaline and serotonin in the spinal cord and increasing hydroxyltryptamine secretion, which resets the body temperature regulation center. Ketamine, a competitive NMDA receptor antagonist has also been shown to inhibit postoperative shivering in many reports.[12-17]

However, there are limited studies on the anti shivering efficacy of prophylactic tramadol compared with low-dose intravenous ketamine. Hence this prospective, randomized, double-blind, placebo-controlled study was designed to compare the effectiveness of 0.5 mg/kg IV ketamine with that of 0.5 mg/kg IV tramadol for the prevention of post-spinal shivering in patients undergoing surgeries under spinal anaesthesia. In addition, side effects between the different treatment groups were also evaluated.

II. Material And Methods

After ethical committee approval and informed consent, this study was performed in 90 patients of ASA grade 1 and 2, belonging to either sex, aged between 18 and 65 years, undergoing surgeries in spinal anaesthesia in a tertiary care centre over a period of Jan 2019 to Feb 2020. Patients suffering from neuromuscular disease, hyperthyroidism, history of cardiopulmonary disease, refusal to participate or temperature >38°C or <36.5°C were excluded from the study. Following a detailed pre-anaesthetic checkup, patients were brought to the Operation theatre and routine monitors attached. The study drug was given by the anaesthetist not involved in the management of the patient and administered by intravenous route just before giving the block. The patients were randomized into three groups of 30 patients each.

- Group C: Patients received 10 mL of 0.9 % normal saline.
- Group K: Patients received ketamine 0.5 mg/kg IV diluted in 10 mL saline
- Group T: Patients received tramadol 0.5 mg/kg IV diluted in 10 mL saline.

The temperature of the OT was maintained at 24±1°C for all the patients. Neuraxial anaesthesia was instituted at L3-L4 interspace using hyperbaric bupivacaine 0.5% with a 23 gauge quincke's spinal needle. During the intraoperative period, after noting the baseline parameters, pulse rate, Non-Invasive Blood Pressure (NIBP), oxygen saturation, temperature and level of sensory block were assessed at 5 min intervals. Sensory block was assessed every 5 min till there was no change in the level of anaesthesia and every 15 min thereafter. The temperature was measured by an axillary thermometer. Shivering was graded using a scale validated by *Tsai and Chu el al.*[18]

- Grade 0 - No shivering,
- Grade 1 - Piloerection but no visible shivering.
- Grade 2 - Muscular activity in only one muscle group.
- Grade 3 - Muscular activity in more than one muscle group but not generalized.
- Grade 4 - Shivering involving the whole body.

During surgery, the shivering scale was recorded at 5 min intervals up to completion of surgery. The prophylaxis was regarded as ineffective if the patients exhibited grade 3 shivering any time during the study and then additional dose of tramadol was administered. Side-effects such as hypotension, nausea, vomiting and hallucinations were also recorded. If patients developed nausea and vomiting, IV metoclopramide 10 mg was administered.

STATISTICAL ANALYSIS

All parameters were analyzed using SPSS 11.0 and STAT 9.0 software. The data among groups were compared using one-way ANOVA. The incidence of shivering and side-effects were compared using the chi-square test. The data was expressed as mean ± SD. A value of $P<0.05$ was considered as statistically significant.

III. Results

The demographic data and surgical duration were comparable in each group. ***(Table 1)***

Table 1: Demographic Data

Parameters (Mean)	Group T	Group K	Group C	P value
Age	43.4 ± 3.4	47.8 ± 2.6	44.6 ± 5.3	0.435
Gender	18 / 12	19 / 11	17 / 13	0.682
Weight	68.6 ± 11.2	69.8 ± 10.8	66.9 ± 11.2	0.789
Height	163.08 ± 10.9	164.10 ± 11.2	163.80 ± 10.8	0.245
Duration of surgery	80.3 ± 11.34	79.9 ± 10.9	78.10 ± 12.5	0.348

The total numbers of patients with intraoperative shivering were significantly less in group K and group T than in group C. In group C, 18 patients reached grade 2 shivering and were subsequently treated with tramodol. In group K and group T only one patient each reached grade 2 shivering ($p<0.001$). At 30 min after spinal anesthesia, there were no differences between the groups regarding grade of shivering. ***(Table 2)***

Table 2: Incidence of Shivering among groups

Time(min)	Grading	Group T		Group K		Group C		P value
		n	%	n	%	n	%	
0	0	28	93.3	28	93.3	18	60	<0.001
	1	02	6.7	02	6.7	03	10	
	2	00	00	00	00	06	20	

	3	00	00	00	00	03	10	
10	0	29	96.6	28	93.3	15	50	<0.001
	1	01	3.3	01	1.3	06	20	
	2	00	00	01	1.3	06	20	
	3	00	00	00	00	03	10	
20	0	27	90	29	96.6	17	56.6	<0.001
	1	02	6.3	01	3.3	04	13.3	
	2	01	3.3	00	00	06	20	
	3	00	00	00	00	03	10	
30	0	29	100	28	90	28	90	0.889
	1	00	00	02	6.6	02	6.6	
	2	00	00	00	00	00	00	
	3	00	00	00	00	00	00	

There was a greater fall in body temperature in the control group as compared with the study drug groups. **(*Table 3*)**

Table 3: Temperature variation among groups

Time (min)	Group T	Group K	Group C	P value
Baseline	37.0 ± 0.4	37.08 ± 0.4	37.0 ± 0.4	0.345
0	36.5 ± 0.4	37.9 ± 0.5	34.6 ± 0.8	0.008
10	36.4 ± 0.7	36.4 ± 0.8	34.9 ± 0.6	0.006
20	36.9 ± 0.5	37.7 ± 0.7	34.3 ± 0.5	0.005
30	36.8 ± 0.4	36.9 ± 0.3	34.4 ± 0.6	0.005

Three patients in Group C, one patient in Group K and six patients in Group T had nausea ($p>0.05$). None of the patients had episodes of oxygen desaturation or respiratory depression during study. Only one patient showed bradycardia after tramadol injection. ***(Table 4)***

Table 4: Incidence of side effects among different groups

Side effect	Group T	Group K	Group C
Respiratory depression	0	0	0
Nausea & vomitting	6 (20%)	1 (10%)	3 (10%)
Bradycardia	1 (3.3%)	0	0

IV. Discussion

Shivering during regional anesthesia is common and can be nearly as severe as that observed during general anesthesia.[19] It can be distressing to the patient and has been cited as one of the primary causes of discomfort during the postoperative period.[9] Intraoperative shivering can be treated by many non pharmalogical methods or pharmological agents. One of the most significant consequence with shivering is an increase in oxygen consumption by up to six times, which can cause rapid oxygen depletion, potentially leading to tissue death.[9,18] Shivering if not treated during intraoperative may impact patient outcomes like prolong recovery and lengthen the period of hospital stay.

In a quest to find a better agent to prevent intraoperative shivering we compared tramadol with ketamine in a placebo controlled study. In our study, the incidence of shivering was 60% (in the placebo group), same findings were reported by *Sagir et al*[20] *Bilotta et al*[21] and *Dhorigol et al.*[22] However, *Sia et al*[23] reported a lower incidence of shivering (40%), but conducted the study under extradural blockade with 15–20 ml of 2% mepivacaine. Moreover it's a known fact that spinal anaesthesia causes a two to three level higher level of autonomic blockade than the sensory level achieved, as compared with extradural blockade, in which autonomic blockade is the same or one level higher than the sensory level achieved. Previous studies investigating the rantishivering properties of ketamine and tramadol have shown similar results as our study. *Sagir et al*[20]also found ketamine in dose of 0.5 mg/kg is effective in controlling shivering under neuraxial blockade.

Dal et al[23] witnessed the similar results of ketamine to prevent shivering under general anaesthesia Whereas, *Gangopadhyay et al*[24] concluded that ketamine 0.5 mg/kg was effective in preventing shivering under spinal anaesthesia. *Bilotta et al* [21] and *Chan et al* [25] found tramadol to be a promising drug in doses of 0.5 mg/kg and 0.25 mg/kg IV respectively in controlling shivering.

Gangopadhyay et al[24] found promising results with tramadol 1.0 mg/ kg IV in preventing shivering under spinal anaesthesia. There was a greater fall in body temperature in the placebo group as compared with the ketamine and tramadol groups in our study. This trend of fall in body temperature is similar with the trends reported by *Sagir et al*[20]. Greater fall in body temperature in the placebo group as compared with the other groups may be because of the study drug effect.

In our study, the incidence of side effects was significantly higher in tramadol group as compared to other groups. *Gangopadhyay et al*[24] also observed a significant number of cases (20/30) of nausea and vomiting

with tramadol like our study. Ketamine is known to cause hallucinations, but none of the patients in any of the groups complained of hallucinations. Studies done in the past support our findings.[20,23]

The major limitation of our study was that we didn't study the hemodynamical changes related to ketamine and sample size taken was relatively low.

V. Conclusion

We conclude that giving either ketamine 0.5 mg/ kg or tramadol 0.5 mg/kg i.v. prophylactically just before neuraxial blockade significantly decreased the incidence of shivering without causing any major side-effects.

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