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Original Research Article

Comparative Study of Tramadol with That of Butorphanol for the Control of Shivering in Patients Undergoing Neuraxial Blockade

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ABSTRACT

Aim: To compare the efficacy of Tramadol with that of Butorphanol for the control of shivering in patients undergoing neuraxial blockade.

Materials And Methods: A randomized, double blind study of 60 patients undergoing lower abdominal and lower limb surgery under spinal anesthesia who got shivering during intra operative period up to 60minutes. Out of which 60 patients, who will develop shivering after neuraxial blockade will be randomly allocated to one of the following groups. Each group contains 30 patients.

Group I: (Tramadol Group) Patients received tramadol intravenously (50mg)

Group II: (Butorphanol Group) Patients received butorphanol intravenously (1mg)

Inclusion criteria: ASA Grade I Or II, age 18 to 60 years, weight 30 to 70 kg, lower abdominal and lower limb surgery under spinal anesthesia.

Exclusion Criteria: Patients not willing to take part in study, ASA grade >2, significant systemic illness, patients with fever, pregnancy, patients with history of seizure, patient on oral anticoagulant therapy, emergency surgeries, conditions where neuraxial blockade will be contraindicated.

Result: Time taken to control Shivering was significantly lower in Group I (Tramadol) as compared to group II (Butorphanol), more patients with higher sedation score with Butorphanol group compared to Tramadol Group, Nausea and vomiting higher in Tramadol Group compared to Butorphanol Group.

Conclusion: Tramadol is most rapid acting & effective in control of shivering with neauraxial block without any significant side effects and least reappearance of shivering as compared to Butorphanol.

Key words: Neuraxial blockade, Tramadol, Butorphanol, Shivering.

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INTRODUCTION

Shivering is defined as readily detectable fasciculation or tremor of face, jaw, head, trunk, or extremities lasting longer than 15 secs.[1] It is an involuntary, oscillatory muscular activity that augments metabolic heat production and it occurs when the balance between heat production and heat loss is disturbed.[2] The reported incidence of shivering following general anaesthesia varies between 5% and 65%.[3] While about 33- 60 % of the patients under regional anaesthesia developed shivering.[3,4] Neuraxial blockade i.e. epidural and spinal anaesthesia decrease the vasoconstriction and shivering threshold to a significant degree.[5] Shivering is not only, uncomfortable to the patients, but it also causes increased oxygen consumption up to 600% above basal level.[6] Shivering leads to increased carbon dioxide production,[7,8] increased cardiac output, tachycardia and hypertension[9,10] raised intraocular pressure,[11] raised intra cranial pressure and lactic acidosis.[12]

Human beings are homoeothermic (warm blooded)[13] where a group of reflex responses are mainly integrated in the hypothalamus to maintain body temperature within a narrow range despite large variations of temperature in external milieu. Homoeothermy is defined by The Thermal Physiology Commission of the International Union of Physiology Sciences as: "A pattern of temperature regulation in which the cyclic variation in core temperature, either nychthermally or seasonally, is maintained within arbitrary limits of $\pm$ 2 ^{0}C despite much larger variation in ambient temperature".[14]

A serious consequence of inadvertent hypothermia is the occurrence of shivering. Heat loss is normally regulated without the major responses of sweating or shivering because autonomic vasoconstriction and dilation usually suffices. Normal thermoregulatory shivering is thus last resort defense mechanism that is activated only when behavioral compensation and maximal

arteriovenous vasoconstriction are insufficient to maintain core temperature.[15] Nearly all patients who are administered general anaesthesia become hypothermic, typically by 1-3^{0}C, depending on the type and dose of anaesthesia, amount of surgical exposure and ambient temperature. In neuraxial anaesthesia, the peripheral, rather than central inhibition of thermoregulatory control is primary cause of hypothermia.[16] During epidural anaesthesia, core temperature decrease by 0.8 $^0 \pm$ O.3 ^{0}C in first hour of anaesthesia. During subsequent 2 hours of anaesthesia core temperature falls an additional 0.4^0 $\pm$0.3^{0}C.[4] Shivering is elicited when the preoptic region of the hypothalamus is cooled.[17] Spinal α motor neurons and their axon are the final common pathway for both coordinated movement and shivering.[18] Reflex activation of α motor neurons via the γ muscle spindle loop is another potential but controversial mechanism that could determine the rhythm and frequency of a motor neuron discharges.[19-21] To prevent shivering non pharmacological methods and pharmacological drugs are used. The non-pharmacological methods are humidifiers,[22] warming mattresses and blankets,[23, 24] radiant heater,[25-28] blood and intravenous fluid warmer, irrigating fluid warmer. The loss of heat can be totally prevented by adequate humidification of inspired gases. The warming mattress has water circulated through plastic thermostatically controlled heater. Hot air mattress used to produce a warm microclimate under surgical drapes and has been reported as effective in reducing heat losses in children. Blood and fluid warmers should be used to maintain their temperature as close to body temperature as possible.[15] In TURP surgery degree of hypothermia induced mainly depends on temperature of irrigating fluid. So it should be warmed before use.[15] Though non pharmacological methods are used to prevent shivering, drugs are used when non pharmacological methods fail. There are different groups of pharmacological drugs like biogenic amines (nor epinephrine and serotonin),[29] cholinomimetics (physostigmine),[30] peptides (met-enkephalines,β endorphines),[31] cations (magnesium sulfate),[32] NMDA receptor antagonists (ketamine), analeptics (methylphenidate, doxapram).[33] Which help in controlling shivering. There are a wide range of opioids and synthetic opioids who have anti-shivering effect like pethidine,[34] tramadol[35] fentanyl,[34] alfentanil,[36] sufentanil,[37] clonidine,[38] and butorphanol.[39,40]

Pure μ receptor agonists, including morphine (2.5mg), fentanyl (25μg), and alfentanyl (250 μg), may be significantly better treatments for post anaesthetic shivering than placebo. [41-43] Addition of various opioids (meperidine, fentanyl) extradurally also reduces the incidence of shivering in parturients who underwent cesarean section under epidural anesthesia[42]. Attempts to treat post-anesthetic shivering have included a range of intravenous drugs (meperidine, tramadol), radiant heaters, increased ambient temperatures, active warming blankets, warm local anesthetic solution or warm intravenous fluids[43]. Meperidine is more effective than equianalgesic concentration of pure μ-receptor agonist.[44] The anti-shivering action of meperidine may be partially mediated by κ-opioid receptors.[45] Meperidine decreases the shivering threshold almost twice as much as the vasoconstriction threshold.[46] The anti-shivering effect of butorphanol is also κ-opioid receptor mediated[47-49]. The effect of opioids on body temperature and thermoregulatory response mediated through their action on preoptic anterior hypothalamus neurons,[50] dorsal raphe nucleus neurons,[51] raphe magnus neurons[52] and spinal cord[53]. Generally, opioid exerts a variety of stimulus effects on signal transduction[54]. They increase formation of CAMP (cyclic adenosine monophosphate) which increases thermosensitivity in warm-sensitive and moderate-slope temperature-insensitive neurons.[55-57]

Tramadol is a good analgesic with powerful anti-shivering properties and share a similar mechanism of action by inhibiting reuptake of 5-HT, nor epinephrine and dopamine.[15] The nucleus raphe magnus is an antishivering center that activates heat loss mechanism and inhibits thermogenesis during cold adaptation.5-HT is the major neurotransmitter in the raphe nuclei, but half of the raphe cells that project to spinal cord are not serotoninergic. There is also a significant amount of norepinephrine in the nucleus raphe magnus.[2]

Aditi A. Dhimar et al[35] found that, tramadol and pethidine were equally efficacious, but tramadol was more potent with respect to control of shivering and its recurrence. It was concluded that I.V tramadol is qualitatively superior to pethidine for control of shivering. Bharat S. et al[39] observed that tramadol takes lesser time to stop shivering than butorphanol. Tramadol controls shivering more effectively than butorphanol without much side effect and sedation. Vogelsang J. et al[40] suggested that butorphanol is an alternative postanaesthetic shaking treatment to meperidine, as it relives shivering within 2 to 5 minutes without producing nausea, vomiting, or recurrence of shivering.

There were studies to compare the effectiveness of pethidine to tramadol as anti-shivering agent or tramadol to butorphanol, but there was no study which compared tramadol, and butorphanol together to find out which drug should be advised for effective control of shivering.

MATERIALS AND METODS

We have undertaken the randomized, double blind study of 60 patients undergoing lower abdominal and lower limb surgery under spinal anesthesia in two year period, who developed shivering during intraoperative period up to 60 mins. The study was conducted in Hi-Tech Medical College And Hospital, Bhubaneswar which is multidisciplinary teaching hospital and approved by the ethical committee of the hospital. The study was randomized by closed envelope method. In this 90 envelops were prepared and sealed, each contains information about either group I, II or III.

Material and Selection of Patient

Consecutively 141 of either sex with ASA grade I and II status posted for elective surgery under regional anesthesia were included in the study. Out of which 60 patients, who developed shivering after neuraxial blockade were randomly allocated to one of the following groups. Each group contains 30 patients.

- **Group I: (Tramadol Group)** Patients were received tramadol i.v. (50 mg)
- **Group II: (Butorphanol Group)** Patients were received butorphanol i.v (1 mg)

Inclusion Criteria

- ASA grade 1 or 2
- Age 18 to 60 years
- Weight up to 30-70 kg
- Lower abdominal and lower limb surgery under spinal anesthesia

Exclusion criteria

- ASA grade >2
- Significant systemic illness
- Allergic reaction to drug
- Patients on MAO inhibitors, tricyclic antidepressant
- Patients with fever, pregnancy
- Patients with history of seizure
- Conditions where neuraxial blockade was contraindicated
- Patients who have received opioid analgesics before surgery
- Patient on oral anticoagulant therapy
- Emergency surgeries.

Patients were evaluated preoperatively and inj. Glycopyrolate 0.2 mg IV was given as a premedication. Preloading of fluid was done with one liter of warm Ringer lactate. Monitors were attached and base line vitals were recorded when patient was taken into operation theatre. Spinal anesthesia was instituted at L3-L4 or L2-L3 interspace in sitting position with spinal needle no.25G. Bupivacaine heavy 0.5% was used for spinal anaesthesia. Surgery was started after achievement of the adequate level of sensory and motor block.

The temperature of the operating room was maintained at 21 ^{O}C—23^{0}C, with a room humidity of approximately 60%. Thermistor was used to record the temperature of the patient. Axillary artery was palpated and temperature probe was fixed over the course of artery in the axillary area and then arm was adducted for continuous measurement of axillary temperature. The volume of I.V. fluid and the use of ephedrine for hypotension were determined by attending anesthesiologists. The administration of pre or intra operative opioids was not permitted. Patients were supplemented with oxygen 6 L/min by face mask during and in the recovery room. Post operatively patients were kept in the recovery room with all monitors attached and covered with sterile blankets. Same temperature and humidity was maintained as in the operation theatre. When patient developed shivering, vitals were noted and its grade was decided as per grading given below.

Table 1: Shivering Grade

Grade 0	**No Shivering**
Grade 1	Mild fasciculations of face or neck, ECG disturbances in absence of voluntary activity of arms.
Grade 2	Visible tremors involving more than one group of muscle.
Grade 3	Gross muscular activity involving the entire body, bed shaking

The sedation score following drug administration was noted as below.

RAMSAY Sedation score

1: Anxious, agitated and restless
2: Cooperative, oriented and tranquil
3: Responsive to commands only.
4: Asleep, but with brisk response to light glabellar tap or loud auditory stimulus
5: Asleep, Sluggish response to light glabellar tap or loud auditory stimuli
6: Asleep no response

The sedation score following drug administration was noted as below.

Nausea and Vomiting Scoring

0: No nausea, vomiting
1: Nausea
2: Vomiting< 2 times in 30 mins
3: Vomiting> times in 30 min
4: Retching

Any patient with nausea and vomiting >2 was treated with ondansetron 4mg i.v. In case of shivering of grade 2 or more lasting for more than 3minute after the procedure, sealed envelope was opened by the senior consultant who was not involved in management of cases and drug was prepared and given to consultant involved in management of patient, who administered the drug. Thus the consultant involved in treating the shivering and also the observer blinded to the drug being used. Consultant having the envelopes marked the patient record and serial No. to randomly allocated group according to study drug. Calculated dose was diluted in 10 ml of distilled water. The dose was given over 60 seconds and the time duration for the complete disappearance of shivering (Grade 2 converted into Grade 0) was noted from the end of the injection. Vitals in the form of temp., pulse, systolic and diastolic blood pressure and SPO_2 were recorded at 0min, 2min, 5min, 10min, 20min, 30min,40min, 60min interval. Any side effects if occurred after giving study drug were also noted and treated by appropriate measures. Same procedure was followed if shivering occurred post operatively. If shivering did not abolished after 15 min of giving study drug, patient was actively warmed by radiant heat warmer. If recurrence (reappearance of shivering after 15 mins following initial response) of shivering occurred, it was noted and treated by actively warming the patient. The sedation score was observed after 10 min of giving the test drug. After completion of the study of 60 patients, data were analyzed by standard statistical method.

Table 2: Demographic data

	Tramadol (N=30)	Butorphanol (N=30)	P	
Age(Yrs)	36.86±13.79	37±13	>0.05	NS*
Sex(M:F)	19: 11	21:9	>0.05	NS*
Weight (Kgs)	48.33±8.33	46.6±6.34	>0.05	NS*
ASA (I:II)	14:16	13:17	>0.05	NS*
Axillary Temp (oC)	36.1 +0.3	36.2 +0.4	>0.05	NS*
Shivering grade	2.27 +0.449	2.3 +0.466	>0.05	NS*
Duration of Surgery (hrs)	2.22 +0.81	2.08 +0.82	>0.05	NS*

*NS= Statistically not significant.

Table 3: Control of shivering

TIME (Minutes)	Tramadol (N=30)	Butorphanol (N=30)	P	
0	16(53.33%)	1(3.33%)	<0.05	*S
2	27(90%)	7(23.33%)	<0.05	*S
5	30(100%)	16(53.33%)		
10	30(100%)	25(83.33%)		
20	30(100%)	30(100%)		
30	30(100%)	30(100%)		
40	30(100%)	30(100%)		
50	16(53.33%)	21(70%)		
60	27(90%)	23(76.66%)		

*S = Statistically significant

Table 4: Hemodynamic

	Tramadol (N=30)	Butorphanol (N=30)	P		
Pre shivering Mean BP	118.6+10.94	119.0+13.0	0.660	>0.05	NS*
Mean PR	83..93 +7.05	85..0 +7.0	0.020	>0.05	NS*
During shivering Mean BP	117.8+10.42	117.0+10.0	0.159	>0.05	NS*
Mean PR	88.23+7.67	90..0 +6.4	1.696	>0.05	NS*
Post shivering Mean BP	118.93+11.37	119.0 +9.7	0.610	>0.05	NS*
Mean PR	85.0 +7.04	85.0 +7.01	0.209	>0.05	NS*

*NS= Statistically not significant; BP= Blood pressure; PR= Pulse rate

Table 5: Recurrence and complications

	Tramadol (N=30)	Butorphanol (N=30)	P	
Recurrence	3(10%)	15(50%)	<0.05	S*
Nausea and vomiting	2(6.66%)	6(20%)	>0.05	NS**

*S= Statistically significant; **NS= Statistically not significant.

RESULTS

In our study, both the groups were comparable with regards to age, weight, gender, and ASA physical status.

There was no significant difference found in the duration of surgery, axillary temperature as well as shivering grades at the start of study between the two groups.

The onset of disappearance of shivering was found at around 1minute and 3 minutes in Group I and Group II respectively. Regarding the disappearance of shivering in both the groups, we found a statistically significant difference as shown in the table-3 and graph-1. Stoppage of shivering occurred earlier in Group I in comparison to Group II (P<0.001) as shown in Table 3.

Haemodynamically there was no significant difference found between the two groups as shown in table 4.

The recurrence of shivering was observed approximately after 50 minutes and the incidence of recurrence was 50% in Butorphanol group while only in 10% in Tramadol group as shown in Table 5.

After repeating the drug shivering had disappeared completely. Complications like nausea and vomiting occurred in 20% in Butorphanol group while only 6.66% in Tramadol group. However the difference is statistically insignificant (P> 0.05).

DISCUSSION

Neuraxial block is a popular technique for lower abdominal. and lower limb surgeries. Approximately 33-60 % of patients undergoing neuraxial block suffer from shivering as reported.[3,4]

The factors causing decrease in core body temperature include, sympathetic block causing peripheral vasodilation, increased cutaneous blood flow resulting in increased heat loss through skin, cold operating room, rapid infusion of cold i.v fluids, direct effect of cold anaesthetic solution upon the thermosensitive structures of spinal cord.[58,59]

Shivering is an unwarranted discomfort under neuraxial block where patients remain quite alert; it increases oxygen consumption up to 600%.[6] Shivering may lead to increased carbon dioxide production,[7,8] increased cardiac output, tachycardia, hypertension[9,10] & increased intra ocular[11] intra cranial pressure, lactic acidosis[12]. Many Opioids like Alfentanyl[34], Tramadol[36] and Butorphanol[39,40] have been used by intravenous or epidural route to prevent or control shivering with varying degree of success reported by many Workers.

Various nonpharmacological and pharmacological methods have been used to prevent body heat loss. Nonpharmacological methods like electrical heaters, forced air warmers, blankets, radiant heat, and warming the operating room suite. The use of warm local anaesthetic solutions or warming of i.v fluids are also effective to reduce shivering.[60,61] Pharmacological methods using Ketanserine Nefopam, Pethidine, Alfentanyl, Doxapram,Tramadol, Clonidine etc have been tried and compared by many studies. These drugs are used effectively when clinically indicated and they are easily available to all centers and prove to be practical in the many settings.

In our study we have compared recently introduced synthetic opioid Tramadol with Butorphanol, which was gold standard for control of shivering. Tramadol a synthetic opioid agonist prevents shivering by inhibiting the reuptake of norepinephrine and

serotonin, hence activating the descending inhibitory spinal pathways. It also modulates the activity of nucleus median raphe acting centrally on the m opioid receptors predominantly with minimal effects on k and d receptors whereas Butorphanol acts through kappa receptors for its anti-shivering effects.

In our study we observed that shivering disappeared by 1 minute in case of Tramadol and 5 minutes in case of Butorphanol and in comparison to earlier study. Furthermore, the complete disappearance of shivering took 10 minutes in Tramadol group and 20 minutes in Butorphanol group. However in our study the complete disappearance of shivering occurred by the end of 5 minutes in case of Tramadol and 20 minutes in Butorphanol group.

Regarding recurrence, shivering reappeared after 50 minutes in 10% patients of Tramadol group and 50 % in Butorphanol Group. The difference was statistically significant ($P<0.05$). Thus various studies including ours there was higher rate of recurrence with Butorphanol in comparison to Tramadol. The probable reason for recurrence of shivering could be result of low plasma concentration of the active drug, when hypothermia is still persisting and individual variations in the core temperatures. Till date it is not clear whether higher shivering grades requires higher doses of the drug.

In our study both the drugs gave good and better haemodynamic stability throughout the course of the study in all the patients. No respiratory depression was observed in any of the cases. Only in 20 % of cases from Butorphanol group had nausea and vomiting which was easily treated with H2 receptor blocker and antiemetic drug.

Bhatnagar S. et al[39] (2001) has also reported that Tramadol has more sustained effect than Clonidine.

CONCLUSION

From our study we conclude that Tramadol is effective in treating shivering under regional anaesthesia due to its rapid onset, effective control, less recurrence rate and minimum side effects, when compared to Butorphanol. Similarly Tramadol was effective and safe in comparison to Butorphanol for control of shivering.

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