

# Comparative Effectiveness of Tramadol, Clonidine & Butorphanol for the Control of Shivering in Patients Undergoing Neuraxial Blockade

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## ABSTRACT

**Aim:** To compare efficacy of tramadol with that of clonidine and butorphanol for the control of shivering in patients undergoing neuraxial blockade.

**Materials & Methods:** Consecutively 200 patients of either sex, age ranges between 18 to 60 years with ASA grade I and II status posted for elective surgery (lower abdominal and lower limb surgery under spinal anesthesia) were included in the study. Out of which 90 patients, who developed shivering after neuraxial blockade during intraoperative period up to 60 mins were randomly allocated to one of the following groups. Each group contains of 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); Group III: (Clonidine Group) Patients were received clonidine i.v (50 mcg).

**Results:** 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 neuraxial block without any significant side effects and least reappearance of shivering as compared to Butorphanol.

**Key words:** Neuraxial Blockade, Tramadol, Butorphanol, Clonidine, Shivering.


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## Article History:

Received: 20-06-2017, Revised: 11-07-2017, Accepted: 26-07-2017

## Access this article online

Website: <a href="http://www.ijmrp.com">www.ijmrp.com</a>	Quick Response code 
DOI: 10.21276/ijmrp.2017.3.4.025	

## INTRODUCTION

Shivering is defined as readily detectable fasciculation or tremor of face, jaw, head, trunk, or extremities lasting longer than 15 secs.<sup>1</sup> 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.<sup>2</sup> The reported incidence of shivering following general anaesthesia varies between 5% and 65%.<sup>3</sup> While about 33- 60% of the patients under regional anaesthesia developed shivering.<sup>3,4</sup> Neuraxial blockade i.e. epidural and spinal anaesthesia decrease the vasoconstriction and shivering threshold to a significant degree.<sup>5</sup> Shivering is not only, uncomfortable to the patients, but it also causes increased oxygen consumption up to 600% above basal level.<sup>6</sup> Shivering leads to increased carbon dioxide production,<sup>7,8</sup> increased cardiac output, tachycardia and hypertension,<sup>9,10</sup> raised intraocular pressure,<sup>11</sup> raised intra cranial pressure and lactic acidosis.<sup>12</sup> Human beings are homoeothermic (warm blooded)<sup>13</sup> 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  $\pm 2$  °C despite much larger variation in ambient temperature".<sup>14</sup>

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.<sup>15</sup> Nearly all patients who are administered general anaesthesia become hypothermic, typically by 1-3°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 thermo-regulatory control is primary cause of hypothermia.<sup>16</sup>

During epidural anaesthesia, core temperature decrease by  $0.8 \pm 0.3$  °C in first hour of anaesthesia. During subsequent 2 hours of anaesthesia core temperature falls an additional  $0.4 \pm 0.3$  °C.<sup>4</sup> Shivering is elicited when the preoptic region of the hypothalamus is cooled.<sup>17</sup> Spinal  $\alpha$  motor neurons and their axon are the final common pathway for both coordinated movement and shivering.<sup>18</sup> Reflex activation of  $\alpha$  motor neurons via the  $\gamma$  muscle spindle loop is another potential but controversial mechanism that could determine the rhythm and frequency of a motor neuron discharges.<sup>19-21</sup> To prevent shivering non pharmacological methods and pharmacological drugs are used. The non-pharmacological methods are humidifiers,<sup>22</sup> warming mattresses and blankets,<sup>23, 24</sup> radiant heater,<sup>25-28</sup> 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.<sup>15</sup> In TURP surgery degree of hypothermia induced mainly depends on temperature of irrigating fluid. So it should be warmed before use.<sup>15</sup> 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),<sup>29</sup> cholinomimetics (physostigmine),<sup>30</sup> peptides (met-enkephalines,  $\beta$  endorphines),<sup>31</sup> cations (magnesium sulfate),<sup>32</sup> NMDA receptor antagonists (ketamine), analeptics (methylphenidate, doxapram).<sup>33</sup> Which help in controlling shivering. There are a wide range of opioids and synthetic opioids who have anti-shivering effect like pethidine,<sup>34</sup> tramadol,<sup>35</sup> fentanyl,<sup>34</sup> alfentanil,<sup>36</sup> sufentanil,<sup>37</sup> clonidine,<sup>38</sup> and butorphanol.<sup>39,40</sup>

Pure  $\mu$  receptor agonists, including morphine (2.5mg), fentanyl (25 $\mu$ g), and alfentanil (250  $\mu$ g), may be significantly better treatments for post anaesthetic shivering than placebo.<sup>41-43</sup> Addition of various opioids (meperidine, fentanyl) extradurally also reduces the incidence of shivering in parturients who underwent cesarean section under epidural anesthesia.<sup>42</sup>

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.<sup>43</sup> Meperidine is more effective than equianalgesic concentration of pure  $\mu$ -receptor agonist.<sup>44</sup> The anti-shivering action of meperidine may be partially mediated by  $\kappa$ -opioid receptors.<sup>45</sup> Meperidine decreases the shivering threshold almost twice as much as the vasoconstriction threshold.<sup>46</sup> The anti-shivering effect of butorphanol is also  $\kappa$ -opioid receptor mediated.<sup>47-49</sup> The effect of opioids on body temperature and thermoregulatory response mediated through their action on preoptic anterior hypothalamus neurons,<sup>50</sup> dorsal raphe nucleus neurons,<sup>51</sup> raphe magnus neurons<sup>52</sup> and spinal cord.<sup>53</sup> Generally, opioids exerts a variety of stimulus effects on signal transduction.<sup>54</sup> They increase formation of cyclic adenosine monophosphate which increases thermosensitivity in warm-sensitive and moderate-slope temperature-insensitive neurons.<sup>55-57</sup>

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.<sup>15</sup> The nucleus raphe magnus is an anti-shivering 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 serotonergic. There is also a significant amount of norepinephrine in the nucleus raphe magnus.<sup>2</sup>

Adit A. Dhimar et al<sup>35</sup> 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<sup>39</sup> observed that tramadol takes lesser time to stop shivering than butorphanol. Tramadol controls shivering more effectively than butorphanol without much side effect & sedation.

Vogelsang J. et al<sup>40</sup> suggested that butorphanol is an alternative post-anaesthetic 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 METHODS

We have undertaken the randomized, double blind study of 90 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 envelopes were prepared and sealed, each contains information about either group I, II or III.

### Patient's Selection

Consecutively 200 patients 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 90 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 received tramadol i.v. (50 mg)
- **Group II: (Butorphanol Group)**  
Patients received butorphanol i.v (1 mg)
- **Group III: (Clonidine Group)**  
Patients received clonidine i.v (50 mcg)

### 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 anaesthesia 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 °C—23°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**

<b>Grade 0</b>	No Shivering.
<b>Grade 1</b>	Mild fasciculations of face or neck, ECG disturbances in absence of voluntary activity of arms.
<b>Grade 2</b>	Visible tremors involving more than one group of muscle.
<b>Grade 3</b>	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, 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 > 2 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 3 minute 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<sub>2</sub> 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**

<b>Groups</b>	<b>Age (years) (mean±SD)</b>	<b>Weight(Kg) (mean±SD)</b>	<b>Surgery Duration (mean±SD)</b>
<b>I (Tramadol)</b>	40.433±10.839	62.700±6.61	1.601±0.579
<b>II (Butorphanol)</b>	39.766±10.937	62.200±6.94	1.683±0.533
<b>III (Clonidine)</b>	39.666±11.13	57.566±2.68	1.916±0.422
<b>P value</b>	<b>P&gt;0.05</b> <b>P=0.416<sup>NS</sup></b>	<b>P&lt;0.05</b> <b>P=0.001<sup>**</sup></b>	<b>P&gt;0.05</b> <b>P=0.051<sup>NS</sup></b>

**Table 3: Control of shivering**

	Gr I (mean±SD)	Gr II (mean±SD)	Gr I (mean±SD)	Gr III (mean±SD)	Gr II (mean±SD)	Gr III (mean±SD)
Mean time taken for complete control of shivering (mins)	2.5333	3.667	2.5333	5.9333	3.667	5.9333
	±	±	±	±	±	±
	0.8996	1.184	0.8996	1.4368	1.184	1.4368
	P<0.05		P<0.05		P<0.05	
	P=0.004		P=0.000		P=0.000	

**RESULTS**

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

The age, weight and duration of surgery in three group were statistically analyzed by ANOVA and DMRT Analysis of variance test and it was found that there was statistical significant difference among the three group for mean weight between the groups (P<0.01).

Paired 't' test is applied to two group at time and the p value is derived.

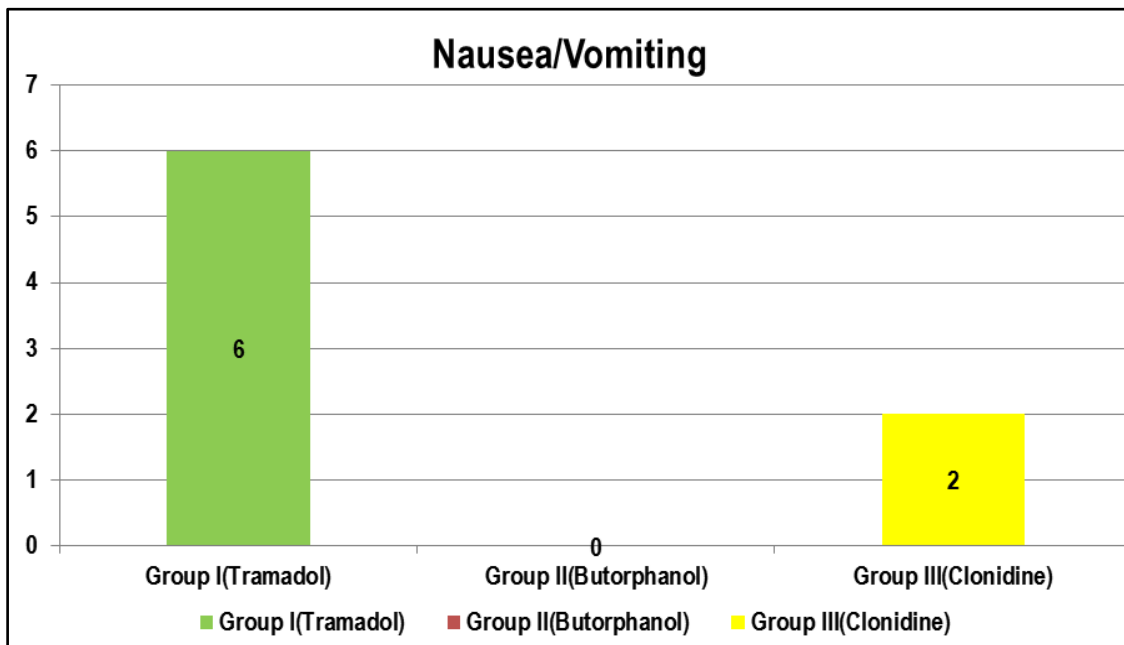
The results show that the difference observed in time taken to stop the shivering among three groups were statistically significant. In group I shivering was controlled earlier compared to group III and group II. Control of shivering was earlier in group II compared to group III.

**Side effects after drug administration**

Nausea and vomiting was appeared in 2 patients in group III and 6 patients in group I. No patient in group II had nausea and vomiting. The appearance of nausea and vomiting were shown in table 4 and figure -1.

**Table 4: Side effect**

Side effects	Gr I	Gr II	Gr II	Gr III	Gr I	Gr III
Nausea & Vomiting	6	0	0	2	6	2
	P<0.05		P>0.05		P<0.05	



**DISCUSSION**

Spinal anaesthesia, a type of central neuraxial anaesthesia is a safe and popular anaesthetic technique used worldwide for various surgeries like lower abdominal and lower limb surgeries. Approximately 33-60 % of patients undergoing neuraxial block suffer from shivering as reported.<sup>3,4</sup> Shivering is an unwarranted discomfort under neuraxial block where patients remain quite alert; it increases oxygen consumption up to 600 %.<sup>6</sup>

Shivering may lead to increased carbon dioxide production,<sup>7,8</sup> increased cardiac output, tachycardia, hypertension<sup>9,10</sup> and increased intra ocular pressure,<sup>11</sup> intra cranial pressure, lactic

acidosis.<sup>12</sup> To obviate this discomfort many authors like Svetlov VA et al.<sup>58</sup> Heid F et al.<sup>59</sup> have used Tramadol even as prophylaxis against shivering. Many Opioids like Alfentanyl,<sup>34</sup> Tramadol,<sup>36</sup> Buprenorphine and Butorphanol<sup>39,40</sup> have been used by intravenous or epidural route to prevent or control shivering with varying degree of success reported by many Workers.

We have compared Tramadol, Butorphanol and Clonidine the most common & efficacious agents for control of shivering in regard to speed of action, effectiveness, reappearance, & associated side effects. These three agents together have compared in few study so far.

Tramadol, a synthetic Opioid agonist prevents shivering by inhibiting reuptake of nor epinephrine and serotonin<sup>15</sup> hence activating descending inhibitory spinal pathways. It also modulates the activity of nucleus- mediated raphe acting centrally on the  $\mu$  receptors. Clonidine and Butorphanol acts through kappa receptors for its anti-shivering effects.

In our study we found 45 % incidence of shivering under Neuraxial block (in 90 patients out of 200 patients). This is comparable to incidence of 33 -60 % as reported by Aditi et al.<sup>35</sup>

We have found that axillary temperature has fallen significantly to  $95.53 \pm 0.57$  from  $98.58 \pm 0.59$  in group I,  $95.70 \pm 0.65$  from  $98.50 \pm 0.50$  in group II &  $95.64 \pm 0.55$  from  $98.55 \pm 0.52$  in group III, this can be explained due to sympathetic block causing peripheral vasodilatation leads to increased heat loss through skin, increased cutaneous blood flow or direct effect of cold anaesthetic solution upon the thermo-sensitive structure of spinal cord or because of cold intravenous solution.

We have found that Tramadol has controlled shivering in  $2.53 \text{ min} \pm 0.89 \text{ min}$  which is comparable to finding of Chen S C et al.<sup>60</sup> This is faster than Clonidine which is  $5.93 \pm 1.43 \text{ min}$  in our study (statistically significant difference) which is in contrast to study by Parvin Sajedi et al<sup>61</sup> who have reported that Clonidine & Tramadol have similar effect in speed & control of shivering. Zehedi et al<sup>62</sup> have also reported faster action of Tramadol than Clonidine, although there mean time was 5 min & 9 min respectively.

The speed of action of Butorphanol in our study is  $3.6 \text{ min} \pm 1.18 \text{ min}$  which is statistically significant slower than Tramadol and is statistically faster than Clonidine. Vogelsang J et al<sup>40</sup> has reported time of 2-5 min with Butorphanol which is similar to our finding.

In our study, we have found that Tramadol has fastest onset of action of anti-shivering effect (2.53 min) as compared to Butorphanol (3.67 min) & Clonidine (5.93min).

Thus we conclude that although all the three agents are equally effective for controlling shivering at 10 min interval, the Tramadol is faster acting followed by Butorphanol & than Clonidine. Although side effects like nausea & vomiting were marginally seen in Tramadol & Clonidine group but did not require any anti-emetic. The other side effects like fall in  $\text{SpO}_2$  & sedation were seen in Butorphanol group. Sedation score was highest with Butorphanol followed by Clonidine & negligible with Tramadol.

## CONCLUSION

From our study we conclude that Tramadol is most rapid acting & effective in control of shivering with neuraxial block without any significant side effects like lowering of  $\text{SpO}_2$ , somnolence & least reappearance of shivering. Clonidine has slowest onset of action & higher rate of reappearance of shivering as compared to Tramadol & Butorphanol, though Butorphanol has little more sedation but is more effective than Clonidine in control of shivering.

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**Source of Support:** Nil. **Conflict of Interest:** None Declared.

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**Cite this article as:** Sheikh Mustak Ali and P.C. Debata. Comparative Effectiveness of Tramadol, Clonidine & Butorphanol for the Control of Shivering in Patients Undergoing Neuraxial Blockade. *Int J Med Res Prof.* 2017; 3(4):124-29. DOI:10.21276/ijmrp.2017.3.4.025