Prophylactic Use of Intravenous Clonidine Compared to Tramadol in Prevention of Intraoperative Shivering under Regional Anesthesia

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Abstract

Objectives: This study aimed to evaluate the relative efficacy of prophylactic intravenous (IV) clonidine and tramadol for control of intraoperative shivering following spinal anesthesia. Materials and Methods: After institutional ethical clearance, 142 patients were chosen from either gender, aged 20–60 years, physical status American Society of Anesthesiology Class I and II scheduled for elective infraumbilical surgery under spinal anesthesia. Patients were randomized into two groups: Group C (n = 71) received injection clonidine 50 µg) IV in 100 ml normal saline (NS) over 10 min and Group T (n = 71) received injection tramadol 50 mg IV. In 100 ml NS over 10 min after spinal anesthesia. Results: Incidence of shivering was not significant when compared between the two groups (P > 0.05). The axillary temperatures fell significantly in Group C from the baseline and remained at a significantly lower level up to 60 min after rescue drug was administered in patients who shivered. There was a similar fall in axillary temperature in Group T in patients having shivering, but the difference was not significant. When compared between the two groups among patients who shivered, the difference in fall of temperature was not significant. Side effects such as hypotension, bradycardia, and sedation were significantly more common in clonidine group, whereas nausea was significantly more common patients of tramadol group. Conclusion: Prophylactic administration of both tramadol and clonidine is effective for controlling shivering under spinal anesthesia. However, tramadol is better because of higher response rate, less sedation, and lesser hemodynamic alterations.

Keywords: Clonidine, shivering, spinal anesthesia, tramadol

INTRODUCTION

Shivering is a common problem during the intraoperative period. It is more frequent and troublesome during regional anesthesia. Around 40%–60% of the patients under regional anesthesia develop shivering.1

Shivering can be very unpleasant and physiologically stressful for the patient. Shivering increases oxygen (O₂) consumption to a level that is produced by light exercise, whereas severe shivering increases metabolic rate and O₂ consumption up to 100%–600%.2 It may induce hypoxemia, lactic acidosis along with a linear increase in carbon dioxide (CO₂) production.3 Ventilation and cardiac output are adversely affected along with adverse postoperative outcomes such as wound infection, increased surgical bleeding, and morbid cardiac events.4 Shivering also increases intraocular pressure and intracranial pressure and creates difficulty in monitoring electrocardiography (ECG), blood pressure (BP), and pulse rate.5 Shivering may be detrimental to the patient with low cardiorespiratory reserve.6 It is uncomfortable to the patient as well as to the operating theater personnel, especially during regional anesthesia.

Shivering depends on various factors, including age, gender, type of anesthesia, volume and temperature of intravenous (IV) fluid, duration of surgery, and temperature of operating theater.6 Human maintains the core body temperature within a narrow physiologic range, but surgery and general anesthesia can alter this delicate balance between heat loss and production.

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by depressing the hypothalamic thermoregulatory center.\[^{[4]}\]
Prolonged impairment of thermoregulatory autonomic control coupled along with the cold environment of operating theaters and infusion of cold fluids contribute to a fall in core body temperature thus, leading to shivering.\[^{[7]}\]

Various methods are now available to control shivering during anesthesia. These include nonpharmacological methods such as the use of radiant heat, covering the patient with blankets to prevent heat loss and warming the operating theater to increase the ambient temperature and use of warm IV fluids.\[^{[8]}\]
Non-pharmacological method using equipment to maintain normothermia are effective but may be expensive and are not practical in all settings. Pharmacological methods include administration of drugs such as opioids (pethidine or tramadol), ketanserin, propofol, granisetron, doxapram, physostigmine, clonidine, and nefopam, but the debate on an “ideal antishivering drug” still continues.\[^{[9]}\]
The problem gets further compounded because of restrictions on drug licensing for opioids like pethidine.\[^{[10]}\]

Tramadol hydrochloride is a synthetic \(\mu\)-opioid receptor agonistic drug. It has a modulatory effect on central monoaminergic pathways, and thus inhibits the neuronal uptake of noradrenaline serotonin and encourages hydroxytryptamine secretion which resets the body temperature regulation center.\[^{[11]}\]
It has demonstrated effectiveness in controlling postspinal shivering.\[^{[12]}\]

Clonidine is an alpha-2 (\(\alpha_2\)) agonist which is highly lipid-soluble and easily crosses the blood-brain barrier.\[^{[13]}\]
It exerts its anti-shivering effects at three levels: Hypothalamus, locus coeruleus, and spinal cord. At hypothalamus, it decreases the thermoregulatory threshold for vasoconstriction and shivering.\[^{[14]}\]
at locus coeruleus -a pro-shivering center in pons, it reduces spontaneous firing, and at the spinal cord level, it activates the \(\alpha_2\)-adrenoreceptors and release of dynorphin, norepinephrine, and acetycholine.\[^{[15-17]}\]

Clonidine is useful in the treatment of postoperative shivering.\[^{[15,16]}\]
Delaunay et al.\[^{[14]}\]
showed that clonidine reduces the thermoregulatory threshold for both vasoconstriction and shivering and suggesting it acts by inhibiting central thermoregulatory control. It is a potent suppressor of sympathoadrenal activity\[^{[15-17]}\]
and has been shown to blunt sympathetic response to surgical stimulation and tracheal intubation. Bradycardia and hypotension are potential adverse effects.\[^{[15,18]}\]

Clonidine is an established antishivering drug and is one of the most frequently used substances in prophylaxis and treatment of shivering. In some studies, sedative and cardiovascular effects of clonidine were noticed when a dose of 3 \(\mu\)g/kg was used. Therefore to minimize adverse effects, we decided to administer 1 \(\mu\)g/kg clonidine. This lower dose of clonidine used in the present study was effective in the prevention of shivering.

Although, both the drugs have been used for control of shivering, studies comparing relative efficacy between the two drugs have shown contrasting findings. While some workers\[^{[19]}\]
are of the view that clonidine offers a better relief against shivering, others\[^{[20]}\]
report in favor of tramadol. In view of these contrasting findings, this study was conducted to compare the relative efficacy of tramadol and clonidine for control of intraoperative shivering under spinal anesthesia.

**Materials and Methods**

This study was conducted at Medical College, Kolkata in the Department of Anaesthesiology. After obtaining approval of the ethics committee and written informed consent from patients, 142 patients from either gender, aged between 20 and 60 years of physical status American Society of Anesthesiology (ASA) Class I and II scheduled for elective infraumbilical surgery under spinal anesthesia were included in this prospective randomized clinical controlled study. Patients presenting with a history of fever, known sensitivity to drugs to be used, shivering even before administration spinal anesthesia and patients requiring supplementation with general anesthesia were excluded from the study.

**Preoperative management**

A detailed preanesthetic checkup of all the patients posted for surgery was performed 1 day before the surgery. All the patients were kept on fast for more 8 h before surgery. On the day of surgery, after the patients were brought to the operation theater (OT), IV line was secured, standard monitors attached and baseline parameters were recorded. Baseline temperature was recorded using a mercury thermometer in the axilla. All the patients were preloaded with Ringer lactate 10 ml/kg before giving neuraxial blockade. All the fluids and drugs were stored and administered at room temperature, and ambient temperature of the operating theater was maintained at 22°C–25°C. Spinal anesthesia was performed with a 25-gauge Quincke spinal needle, in a sitting position, at the L3–4/4–5 interspace (midline approach) with bupivacaine (0.5%, heavy) in a dose of 3.5 ml, to achieve a desirable level at T8–T10 dermatome, in accordance with the surgical procedure.

The patients were randomly allocated to two groups: Group C \((n = 71)\) received injection clonidine 50 \(\mu\)g IV in 100 ml normal saline (NS) over 10 min after administration of spinal anesthesia and Group T \((n = 71)\) received injection tramadol 50 mg IV in 100 ml NS over 10 min after spinal anesthesia.

Grading of shivering was done as per wrench,\[^{[21]}\] which is as follows: Grade 0: No shivering, Grade 1: One or more of the following: Piloerection, peripheral vasoconstriction, peripheral cyanosis with, but without visible muscle activity, Grade 2: Visible muscle activity confined to one muscle group, Grade 3: Visible muscle activity in more than one muscle group, Grade 4: Gross muscle activity involving the upper part of body. The attending anesthetist recorded the frequency of shivering during the operative period after spinal anesthesia. A number of complete responders – (cases with no shivering) were recorded. A number of cases of shivering and the time
of appearance of shivering after administration of the drug was noted.

In patients who developed hypotension (fall in BP >20% of the baseline value) were treated with IV fluid and injection mephenetermine (6–10 mg.) IV bolus. Patients who developed bradycardia (heart rate <60 beats/min) were given atropine 0.6 mg IV. Duration of surgery was noted. Recurrence of shivering was also observed until the patient left the OT. Any patient who developed shivering despite drug administration (clonidine or tramadol) were managed with rescue dose of tramadol 50 mg IV bolus. Side-effects and complications such as nausea, vomiting, hypotension, bradycardia, allergic reactions, and sedation if present, were recorded. If patients develop nausea and vomiting, metoclopramide 10 mg IV was administered.

Sample size and statistical methods
We planned the study with independent cases in each group arranged in a 1:1 ratio. Prior data from a similar study indicated that the failure rate to prevent shivering by clonidine was 0.466, whereas, it was 0.266 for tramadol.[20] So to able to reject the null hypothesis that the failure rates for both the groups were equal with probability (power) of 0.7, we required to study 71 patients in each group. The Type I error probability associated with the test of null hypothesis was set at 0.05. The sample size was calculated using power and sample size calculated version 3.1.2, 2014.[22]

Observation and results were evaluated and compared between the two groups using SPSS version 18 (SPSS Inc., Released 2009, PASW statistics for windows, Chicago, USA). Numerical variables were presented as mean with standard deviation, whereas categorical variables were presented as percent. As regard numerical variables; independent sample t-test was performed. Moreover for categorical variables, Chi-square test was performed. P < 0.05 was considered statistically significant.

Results
There were no statistically significant differences between the two groups in terms of demographic characteristics, namely, age, sex, weight, height, body mass index (BMI), ASA status, Mallampati score (MPS), and duration of surgery as shown in Table 1.

No statistically significant differences were seen between the two groups in terms of demographic characteristics, namely, age, sex, weight, height, BMI, ASA status, MPS, and duration of surgery (P > 0.05).

When compared between the two groups throughout the period of observation, there was no significant difference in axillary temperature.

The axillary temperature fell significantly in Group C from the baseline value and remained at a significantly lower level up to 60 min after rescue drug was administered. However, although there was a similar fall in axillary temperature in Group T, the difference was not significant probably due to small sample size of patients who had shivering (two patients).

When compared between the two groups among patients who shivered, although there was a fall in axillary temperature during shivering in both the groups, the difference in fall of temperature was not significant when compared between the two groups.

Side effects such as hypotension, bradycardia, and sedation were significantly more common in clonidine group, whereas nausea was significantly more common patients of tramadol group.

Discussion
Shivering is an involuntary, oscillatory muscular activity which occurs as a thermoregulatory response to hypothermia in an attempt to augment the metabolic heat production.[23] Spinal anesthesia inhibits central thermoregulating control through blockade of the peripheral sympathetic nervous system and motor nerves, thus, abolishing vasconstriction and shivering in the region of the body below the level of block achieved after drug administration.[24] As a consequence, patients posted for major and or prolonged surgical procedures under regional anesthesia are at increased risk of developing severe hypothermia.[25] Its magnitude varies according to patients’ initial thermal status and may be attenuated by warming lower limbs beforeesthetic induction.[26]

Usually, body areas free from sympathetic and motor block trigger a compensatory thermoregulating response when lowered shivering threshold is reached. However, shivering restricted to upper extremities is relatively ineffective and insufficient to prevent additional hypothermia.[27] It only increases patient’s discomfort and causes further common perioperative problems by causing hypertension, tachycardia, and increase metabolic demands as well as interference in patient monitoring like ECG.

Several nonpharmacological and pharmacological methods have been employed to prevent heat loss and decrease shivering. Nonpharmacological methods include radiant

| Table 1: Demographical profile of the patients of both the groups |
|------------------|---------------|---------------|-----|
| Groups           | Group C       | Group T       | P   |
| Age (years), mean±SD | 41.68±9.80   | 42.38±9.31    | 0.66|
| Sex (male/female) | 35/36         | 41/30         | 0.32|
| Weight (kg), mean±SD | 56.08±3.15   | 56.55±3.52    | 0.41|
| Height (m), mean±SD | 1.58±0.09    | 1.60±0.07     | 0.27|
| BMI (kg/m²), mean±SD | 22.48±2.27   | 22.16±1.49    | 0.32|
| Physical status ASA class I/II | 34/37 | 42/29         | 0.18|
| MPS I/II          | 36/35         | 34/37         | 0.74|
| Duration of surgery (min), mean±SD | 74.22±5.03 | 75.04±8.06 | 0.47|

SD=Standard deviation, MPS=Mallampati score, BMI=Body mass index, ASA=American Society of Anesthesiology

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The study was designed to compare the efficacy of prophylactically administered clonidine, an α2 adrenoceptor agonist, with that of prophylactically administered tramadol, an opioid analgesic for control of intraoperative shivering after spinal anesthesia in patients undergoing lower limb and lower abdominal surgeries.

According to the study by Mohta et al.,[28] three doses of tramadol, that is, 1, 2, and 3 mg/kg were effective for prophylaxis of postanaesthetic shivering. Since the adverse effects, nausea, in particular, are dose-dependent; therefore, it is more likely to appear if the loading dose is high.[29] Hence, in our study, we selected the dose of tramadol as 50 mg.

Various studies have established the role of clonidine as an antishivering agent.[14,30,31] During some of the related studies, sedative effects of clonidine were noticed when a dose of 3 µg/kg was used.[30,31] However, some studies revealed that even a lower dose of clonidine was effective in the reduction of shivering.[14,16,32-34] Therefore, to minimize adverse effects, we decided to administer clonidine in a dose of 50 µg. This lower dose of clonidine used in this study was effective in the prevention of shivering but still had sedative potential.

In this study, both groups were comparable with regard to demographic characteristics, that is, age, sex, weight, height, BMI, ASA status, MPS, and duration of surgery [Table 1].

More patients receiving clonidine developed shivering as compared to patients who received tramadol (Group C = 5 vs. Group T = 2). The time of onset of shivering and grade of shivering was similar in both the groups. However, this study showed that the time taken for control of intraoperative shivering was less in tramadol group and showed statistically significant difference from clonidine group when rescue drug (tramadol) was administered to control intraoperative shivering [Table 2].

It was 5.20 ± 1.30 min and 2.50 ± 0.70 min in clonidine and tramadol group, respectively (P = 0.04) [Table 2], and was comparable to the previous study by Bansal and Jain,[20] Reddy and Chiruvella,[35] and Talakoub and Meshkat.[36]

With respect to axillary temperature, the two groups did not differ from each other significantly when compared between the two groups throughout the period of observation [Table 3]. However, when axillary temperatures were compared from baseline within the two groups in patients who shivered, a significant fall (P < 0.05) in axillary temperature was observed in Group C which remained at a significantly lower level up to 60 min after rescue drug was administered [Table 4]. However, although there was a similar fall in axillary temperature in Group T, the difference was not significant probably due to small sample size of patients who had shivering (two patients).

When compared between the two groups among patients who shivered, although there was a fall in axillary temperature during shivering in both the groups, the difference in fall of temperature was not significant when compared between the two groups [Table 5].

In this study, there was no significant difference in the pulse rate, systolic and diastolic BP between the two groups in their baseline values. During shivering, there was a minimal increase in pulse rate (approximately 12% from baseline value) and BP (approximately 9%) in both the groups. However, after drug administration, there was a minor fall in hemodynamic parameters in both groups with a higher fall in pulse rate and BP in clonidine group compared with the tramadol group at various time intervals. A study by Bansal and Jain,[20] supports our findings.

Significantly, more patients who received clonidine developed hypotension (Group C = 19.72% compared to Group T = 1.41%) and bradycardia (Group C = 11.27% compared to Group T = 1.41%) as compared to those who received tramadol. Four patients receiving clonidine developed dry mouth, whereas none of the patients who received tramadol developed dry mouth [Table 6].

There was statistically significant difference in number of patients who were sedated (17) among both groups, with a higher number of patients becoming sedated in Group C than Group T [Table 6].

None of the patients among clonidine group complained of nausea or vomiting, whereas in tramadol group, 16.9% of patients complained of nausea and 4.22% of patients had vomiting [Table 6]. Our findings were comparable to Maheshwari et al.[37] and Joshi et al.[38] study.

**Conclusion**

To conclude, prophylactic administration of both tramadol hydrochloride and clonidine are effective for control of
Table 3: Comparison of axillary temperature at different time intervals between the two groups

| Group (n=71, both Group C and T) | Mean±SD  | P    |
|----------------------------------|----------|------|
| Baseline                         |          |      |
| Group C                          | 98.41±0.16 | 0.25 |
| Group T                          | 98.38±0.16 |      |
| Postspinal                       |          |      |
| Group C                          | 98.40±0.16 | 0.14 |
| Group T                          | 98.36±0.16 |      |
| 15 min postspinal                |          |      |
| Group C                          | 98.26±0.31 | 0.65 |
| Group T                          | 98.49±0.12 |      |
| 30 min postspinal                |          |      |
| Group C                          | 98.33±0.10 | 0.64 |
| Group T                          | 98.49±0.12 |      |
| At the end of procedure          |          |      |
| Group C                          | 98.33±0.10 | 1.00 |
| Group T                          | 98.33±0.10 |      |

Table 4: Comparison of axillary temperature from baseline within the two groups in patients who shivered

| Comparison parameter (baseline) | Group C (n=5) | Group T (n=2) | P    |
|---------------------------------|---------------|---------------|------|
| Postspinal                      | 0.37          | 0.20          |      |
| During shivering                | 0.001         | 0.10          |      |
| 15 min after drug               | 0.01          | 0.30          |      |
| 60 min after drug               | 0.03          | 0.50          |      |

Table 5: Comparison of axillary temperature between the two groups among patients who shivered

| Group               | Mean±SD     | P    |
|---------------------|-------------|------|
| Baseline            | Group C     | 98.52±0.11 | 0.85 |
|                     | Group T     | 98.50±0.14 |      |
| Postspinal          | Group C     | 98.48±0.11 | 0.09 |
|                     | Group T     | 98.20±0.28 |      |
| During shivering    | Group C     | 97.24±0.38 | 0.85 |
|                     | Group T     | 97.30±0.14 |      |
| 15 min after drug   | Group C     | 98.08±0.30 | 0.93 |
|                     | Group T     | 98.10±0.14 |      |
| 60 min after drug   | Group C     | 98.28±0.18 | 0.41 |
|                     | Group T     | 98.40±0.00 |      |

Table 6: Side effects

| Complications        | Number of patients (%) | Group C | Group T | P    |
|----------------------|------------------------|---------|---------|------|
| Nausea               | 12 (16.90)             | 0       | 0       | 0.00 |
| Vomiting             | 3 (4.22)               | 0       | 0       | 0.08 |
| Hypotension          | 14 (19.72)             | 1       | 1 (1.41)| 0.00 |
| Bradycardia          | 8 (11.27)              | 1 (1.41)| 0.02   |
| Dry mouth            | 4 (5.63)               | 0       | 0.43   |
| Sedation score 2 or more | 42 (59.15)     | 14 (19.72)| 0.00  |

shivering under spinal anesthesia. However, tramadol hydrochloride is better as compared to clonidine due to higher response rate, less sedation, and lesser hemodynamic alterations. However, nausea and vomiting are more in tramadol group, but they are controllable.

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Conflicts of interest
There are no conflicts of interest.

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