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A Comparative Evaluation of Dexmedetomidine and Tramadol for Control of Post-spinal Anesthesia Shivering

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Abstract

Study Objective: Primary aim was to compare and study the efficacy of intravenous dexmedetomidine (1 *µg/kg*) and tramadol (1 *mg/kg*) when used for the control of post-spinal anesthesia shivering. We also compared and studied the hemodynamic changes, complications and adverse effects, in both study groups. *Design:* Prospective randomised double blind study. *Setting:* Operating room. *Patients:* Sixty American Society of Anesthesiologists Grade I and II patients of either gender, aged between 18 and 60 years, scheduled for various surgical procedures under sub-arachnoid block. *Interventions:* The patients were randomised in two Groups of 30 patients each to receive either 1 *µg/kg* dexmedetomidine (Group D) or 1 *mg/kg* tramadol (Group T) as a slow intravenous bolus over 10 minutes, once shivering commenced. *Measurements:* Grade of shivering, onset of shivering, time for cessation of shivering, recurrence, response rate (complete. Incomplete or failure to control shivering), duration of surgery and spinal anesthesia, axillary temperature, hemodynamic parameters (heart rate, systolic, diastolic and mean arterial pressure, ECG) and adverse effects were observed at scheduled intervals. *Results:* The mean time taken for cessation of shivering in Group D was 2.55 ± 1.06 minutes, whereas that in Group T was 4.15 ± 1.68 minutes. The difference between the two Groups was analyzed quantitatively and found to be highly significant ($p < 0.001$). In dexmedetomidine Group, 2 patients had recurrence; whereas, in tramadol Group, 5 patients had recurrence. *Conclusion:* Both dexmedetomidine (1 *mg/kg*) and tramadol (1 *mg/kg*) are effective in treating patients with post-spinal anesthesia shivering. However, dexmedetomidine is more effective as time taken for complete cessation of shivering is shorter with dexmedetomidine as compared to tramadol and incidence of recurrence of shivering is also lower. Furthermore, dexmedetomidine does not cause adverse effects like nausea and vomiting as are seen with tramadol. Sedation caused by dexmedetomidine provides additional comfort to the patient.

Keywords: Shivering; Tramadol; Dexmedetomidine; Anesthesia; Spinal.

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Introduction

Shivering is known to be a frequent complication, reported in 40 to 70% of patients undergoing surgery under spinal anesthesia.[1,2] Spinal anesthesia significantly impairs the thermo regulatory system by inhibiting tonic vasoconstriction which plays a significant role in temperature regulation. It is associated with greater heat loss than general anesthesia which is attributed to various reasons like abnormal heat loss due to vasodilatation, impairment of shivering in the area of block and rapid intravenous (IV) infusion of cold fluids.[3]

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Shivering is a very unpleasant and physiologically stressful experience for the patient undergoing surgery, and some patients find the accompanying cold sensation to be worse than post-operative surgical pain. Excessive shivering creates an imbalance between oxygen demand and supply ratio. The resultant increased demand, (sometimes up to six times the normal) and relative deficit of oxygen supply can lead to various metabolic derangements such as hypoxemia, lactic acidosis and hypercarbia, thereby, hampering smooth recovery from anesthesia.[4] This can be detrimental in certain groups of patients; including those with raised intraocular pressure, intracranial tension, and patients with limited cardiovascular reserve.[5,6]

There are various pharmacological and non-pharmacological methods available to control shivering during anesthesia. During the last decade, tramadol, a synthetic opioid, has become a favored and commonly used drug for post-spinal shivering. The anti-shivering action of tramadol is probably mediated via its serotonergic reuptake inhibition and noradrenergic activity or both.[7-9] However, it has some adverse effects like nausea, vomiting and dizziness.

Dexmedetomidine, is a highly selective α2 adrenoceptor agonist which exhibits anti-shivering property by binding to α2 receptors that mediate vasoconstriction. It is also postulated that it lowers shivering threshold through its centrally mediated action on the hypothalamus.[10,11] It is devoid of adverse effects like nausea and dizziness, but has been reported to cause bradycardia, hypotension and sedation in some patients.

This study compared the efficacy of dexmedetomidine and tramadol in the treatment of postspinal anesthesia shivering as well as their sideeffect profile.

Materials and Methods

This was a prospective, randomised, doubleblind study, which was conducted at a tertiary care centre after taking approval from Institutional Ethics Committee. All subjects gave written informed consent to participate in the study. The study protocol followed the guidelines stated by the Consort criteria.

Taking a significance level of 5%, power of 80%, and using the time to disappearance of shivering after medication, from a similar study,[12] sample size was calculated using Winpepi Statistical Package.

Sixty American Society of Anesthesiologists (ASA) Grade I and II consenting patients of either gender aged 18–60 *years* scheduled for elective as well as emergency lower abdominal, lower limb, orthopedic and plastic surgeries under spinal anesthesia were included in the study. Patients with known hypersensitivity to dexmedetomidine or tramadol, significant medical comorbidities, known history of substance or alcohol abuse, patients receiving any premedication, and patients with initial body temperature > 38 °C or < 36 °C were excluded from the study.

All patients who fulfilled the inclusion criteria and developed postspinal anesthesia shivering were enrolled and randomised using computer generated chart with allocation ratio of 1:1 into either of the two Groups. Group D (n = 30) were administered dexmedetomidine 1 *μg/kg* intravenous (IV) and Group T (n = 30) received tramadol 1 *mg/kg* IV as per randomisation by an anesthesiologist (not a part of the study) who prepared either of the drugs, at the onset of shivering. The anesthesiologist conducting the case as well as recording the data were unaware of the drug being administered.

After thorough pre-anesthetic checkup, patients were taken into the operation theatre. IV access was secured with 20-gauge cannula, monitoring devices were attached (these included heart rate, pulse oximeter, ECG, non-invasive BP, temperature probe), and baseline parameters were recorded. The subjects were pre-loaded with 10 *ml/kg* Ringer's Lactate fluid and maintained on IV fluids throughout the procedure.

Spinal anesthesia was given in the sitting position with due aseptic precautions. After painting and draping of the lumbar area, a 26 G Quincke's spinal needle was introduced in L3-L4 inter-vertebral space. CSF free flow was confirmed and sub-arachnoid block was administered with 0.5% heavy bupivacaine (3–3.5 *ml*) to achieve the desired level at T5-T6 dermatome, in accordance with the surgical procedure. All operation theatres were maintained at an ambient temperature of around 24°C–25°C. Supplemental oxygen was administered to all the patients at the rate of 2 l *min* with Hudson's face mask and patients were covered with drapes but not actively warmed. IV fluids and drugs were administered at room temperature.

After induction of spinal anesthesia, patients were observed for the occurrence of shivering until the post-operative period. Shivering was graded using a four point scale as per Wrench:[13]

- Grade 0: No shivering;
- Grade 1: One or more of the following:

Piloerection, peripheral vasoconstriction, peripheral cyanosis, but without visible muscle activity;

- Grade 2: Visible muscle activity confined to one muscle group;
- Grade 3: Visible muscle activity in more than 1 muscle group;
- Grade 4: Gross muscle activity involving the whole body.

Patients who developed either Grade 3 or 4 shivering lasting for a minimum period of 2 *minutes*, were included in the study. Injection Dexmedetomidine 1.0 *mcg/kg* or Injection Tramadol 1.0 *mg/kg* were diluted to a volume of 10 *ml* in a 10 ml syringe and presented as coded syringes as per randomisation list by an anesthesiologist who was unaware of the group allocation. This was then administered to the patient as a slow IV injection over a period of 10 *minutes*. The attending anesthesiologist recorded the time in minutes at which shivering started after spinal anesthesia (onset of shivering), time of administration of the test drug, and time to the disappearance of shivering.

Shivering control was defined as 'complete' when post-treatment, the shivering score declined to 0; 'incomplete' when the scores decreased, but did not abolish the shivering completely; and 'failed' if no change in scores was observed.

Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, oxygen saturation, ECG, axillary temperature and Wrench's shivering grades were recorded at 0, 1, 2, 5, 10, 15 and 30 *minutes* after administering the test drug.

Duration of surgery was recorded and duration of spinal anesthesia was noted by assessing spontaneous recovery of sensory block using the pin-prick method and observing spontaneous movements of limbs in the post-operative period. Recurrence of shivering was also noted.

In case, there was recurrence of shivering, patients were treated with an additional dose of dexmedetomidine (0.5 *µg/kg* IV) or tramadol (0.5 *mg/kg* IV) in the respective groups and/or active warming measures using convection heaters or infusing moderately warm IV fluids.

Adverse effects such as nausea, vomiting, dizziness, sedation, bradycardia (heart rate < 50 *beats/minute*) and hypotension (fall in systolic blood pressure > 20% of baseline) were watched for and recorded.

Nausea and vomiting were treated with injection metoclopramide 10 *mg* IV as and when required. Bradycardia, if it occurred, was treated with a bolus dose of Inj Atropine 0.6 *mg* intravenously. Whereas, hypotension was treated with intravenous Inj Mephenteramine 6 *mg* increments.

Sedation was assessed as per the modified Ramsay Sedation Scale:[14]

- Grade 1: Patient anxious or agitated or both;
- Grade 2: Patient co-operative, oriented and tranquil;
- Grade 3: Patient response to commands only;
- Grade 4: A brisk response to light glabellar tap;
- Grade 5: A sluggish response to a light glabellar tap;
- Grade 6: No response.

Sedation score > Grade 3 was termed as sedation.

The coding was opened after completion of the study to compile results. Data was collected, compiled and tabulated. The statistical analysis was done using parametric test and the final interpretation was based on Z - test (standard normal variant) with 95% level of significance.

Quantitative data was analysed by Student '*t*' test. Qualitative data was analyzed by Chi-square test.

Results

In the present study, a total of 60 patients out of 85 consecutive patients met the inclusion criteria and consented for study. These 60 patients were randomized into two Groups of 30 each. As it was an intraoperative study, no patient was lost to followup, (Diagram 1).

Both groups were comparable with respect to age, gender, weight, ASA grade, duration of surgery and the duration of spinal anesthesia, (Table 1).

Table 1: Demographic profile of patients of both groups

Parameter	Group D (n = 30)	Group T (n = 30)	*p* - value
Gender (Male/ Female)	14/16	15/15	
Age (years)	37.43 ± 11.09	37.33 ± 11.33	0.97
Weight (kilograms)	63.43 ± 12.71	61.07 ± 11.57	0.45
Duration of surgery (minutes)	64 ± 6.35	63.1 ± 5.05	0.55
Duration of spinal anesthesia (minutes)	232.77 ± 13.58	226.97 ± 11.94	0.08

There was no statistically significant difference in time for the onset of shivering between the two groups.

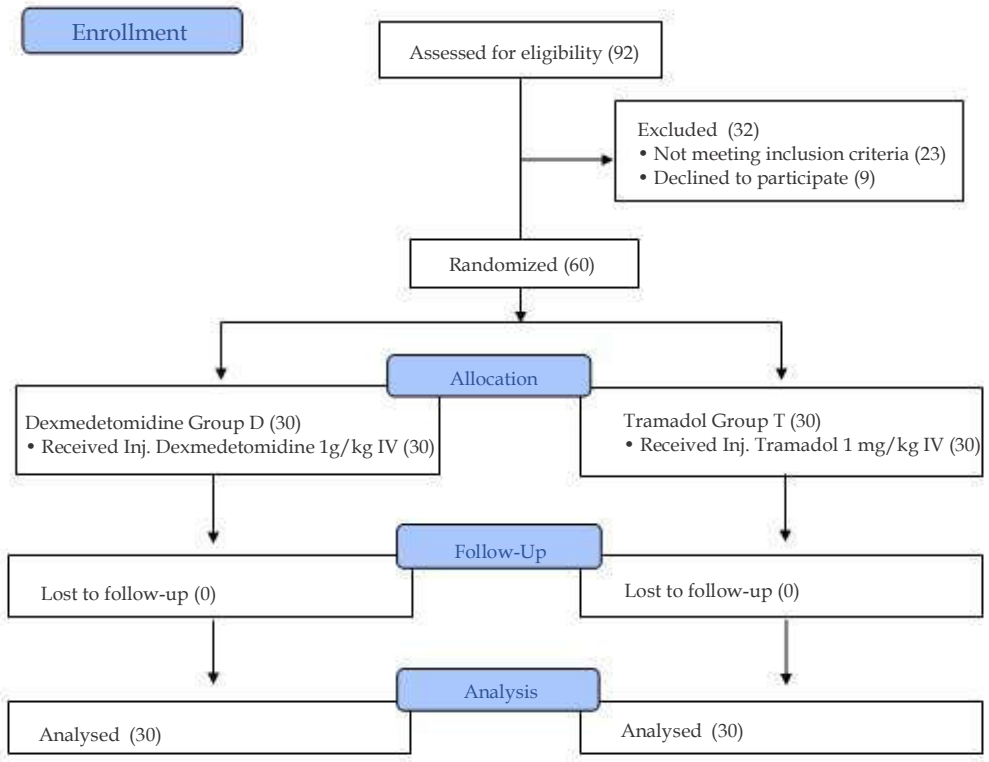

Diagram 1: Participant Flow Diagram

The mean time taken for cessation of shivering in Group D was 2.55 ± 1.06 *minutes*, whereas that in Group T was 4.15 ± 1.68 *minutes*. The difference between the two Groups was analyzed quantitatively and found to be highly significant ($p < 0.001$), thereby, proving that dexmedetomidine gave faster control of shivering than tramadol.

Also, in dexmedetomidine Group, 26 patients had complete cessation of shivering; 3 had incomplete control, and in 1 patient the drug failed to control shivering. In tramadol Group, 22 subjects had complete control of shivering; 5 had incomplete control, and 3 failed.

In dexmedetomidine Group, 2 patients had recurrence; whereas, in tramadol Group, 5 patients had recurrence. The incidence of recurrence of shivering with dexmedetomidine was lower than that with tramadol, (Table 2).

Table 2: Parameters for post-spinal anesthesia shivering

Parameter	Group D	Group T	*p* - value
Onset of shivering (*minutes*)	29 ± 6.33	29.7 ± 5.98	0.66
Time for control of shivering after medication (*minutes*)	2.55 ± 1.06	4.15 ± 1.68	< 0.001
Response rate (%)			
Complete	86.67	73.33	
Incomplete	10	16.67	
Failed	3.33	10	
Recurrence (number of patients)	2	5	

A different set of side effects was seen in each Group. In dexmedetomidine Group, out of 30 patients, 4 patients had hypotension, 3 patients had bradycardia, 3 patients were sedated (modified Ramsay Sedation score > 3) and 1 patient developed dryness of mouth. None of the subjects in tramadol Group developed these side effects. In tramadol Group, 11 patients had nausea, 3 patients had vomiting and 6 patients had dizziness following administration of test drug. In dexmedetomidine Group, none of the patients had nausea, vomiting or dizziness, (Table 3).

Table 3: Pattern of side effects in both groups

Side Effect	Group D (Number of patients)	Group T (Number of patients)
Hypotension	4 (13.33%)	0
Bradycardia	3 (10%)	0
Sedation	3 (10%)	0
Dry Mouth	1 (3.33%)	0
Nausea	0	11 (36.67%)
Vomiting	0	3 (10%)
Dizziness	0	6 (20%)

Respiratory depression, allergic reaction or itching were not seen in any of the patients of either group.

Discussion

Shivering is defined as an involuntary, repetitive activity of skeletal muscles. It is a common post-anesthesia adverse event with an incidence of 40–70% following spinal Anesthesia.[15]

Spinal anesthesia impairs the thermoregulation by inhibiting vasomotor and shivering responses and by redistribution of heat from core to periphery of the body resulting in hypothermia.[16] It is a physiological response to a fall in core temperature in an attempt to raise the metabolic heat production. It increases oxygen demand, heart rate, cardiac output, causes lactic acidosis, increased intraocular pressure, increased intracranial pressure, increased carbon dioxide production, increased hemodynamic changes and increased pain perception. Thus, it may lead to adverse outcomes in patients with low cardio pulmonary reserve.

Non-pharmacological methods to prevent and treat shivering include warming blankets, warm operation theatre, warmed intravenous fluids, heated and humidified inspired gases, and increasing ambient air temperatures.

The neurotransmitter pathways involved in shivering are multiple and involve opioids, Alpha-2 adrenergic, serotonergic, and anticholinergic receptors. Hence, drugs acting on these systems which include opioids (pethidine, nalbuphine, or tramadol), ketanserin, propofol, doxapram, clonidine, ketamine and nefopam are utilized in the treatment of shivering. However, adverse effects such as hypotension, hypertension, sedation, respiratory depression, nausea and vomiting limit their use. Hence, the hunt for an ideal anti-shivering agent is continuing.

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine. Tramadol is an opioid analgesic with opioid action mediated via μ receptor with minimal effect on kappa and delta binding sites; tramadol also activates the mononergic receptor of the descending neuraxial inhibiting pain pathway. The anti-shivering action of tramadol is probably mediated via its opioid or serotonergic and noradrenergic activity or both. During the last decade, tramadol has become a favored and commonly used drug for post-spinal anesthesia shivering. However, it has adverse effects like nausea, vomiting, dizziness etc., which cause further discomfort to the patient.[17]

Dexmedetomidine, a congener of clonidine, is a highly selective α_2 adrenoceptor agonist. It has been used as a sedative agent and is known to reduce the shivering threshold. Few studies which have explored its anti-shivering potential have inferred that dexmedetomidine is an effective drug without any major adverse effect and provides good hemodynamic stability.[18–20]

The anti-shivering effects of alpha adrenoceptor agonists are mediated by binding to alpha-2 receptors that mediate vasoconstriction and the anti-shivering effect. In addition, it has hypothalamic thermoregulatory effects.[21] Dexmedetomidine comparably reduces the vasoconstriction and shivering thresholds, thus suggesting that it acts on the central thermoregulatory system rather than preventing shivering peripherally.[10]

The desired properties of a drug to prevent shivering include easy availability and minimal side effects. Till now, no ideal drug is known that can be used to treat post-spinal anesthesia shivering.

In our study, in Group D, 26 patients (86.67%) had complete cessation of shivering; 3 (10%) had incomplete control, and in 1 patient (3.33%) the drug failed to control shivering. In Group T, 22 subjects (73.33%) had complete control of shivering; 5 (16.67%) had incomplete control, and 3 (10%) failed. These findings differed from those of Kundra *et al*. who found that shivering disappeared in all patients who were given dexmedetomidine or tramadol.[12]

Venkatraman *et al*. compared tramadol, clonidine and dexmedetomidine for the treatment of post spinal anesthesia shivering using a lower dose of dexmedetomidine than that in our study. Dexmedetomidine gave the fastest results (5.7 ± 0.79 *minutes*), followed by tramadol (6.76 ± 0.93 *minutes*) and clonidine being the slowest (9.43 ± 0.93 *minutes*).[22]

The findings of Mittal G *et al*. correlate well with those of our study, in that, there was recurrence of shivering in 1 patient out of 25 (4%) in dexmedetomidine Group and 2 patients out of 25 (8%) in tramadol Group.[23]

Bradycardia and hypotension is a frequently reported adverse effect of α_2 adrenoceptor agonists. Verma NK *et al*. reported that hypotension was observed in highest number of patients (33.33%) in Clonidine, 20% of Dexmedetomidine Group, but only 10% of Tramadol Group, which is significant.[24]

We observed that while heart rate and mean arterial pressure were lower following administration of dexmedetomidine than

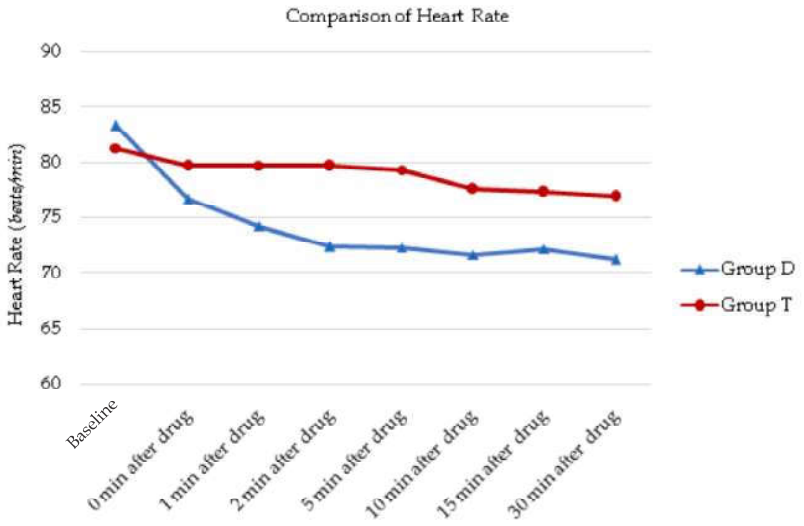

Figure 2: Line diagram showing comparison of heart rate in study groups

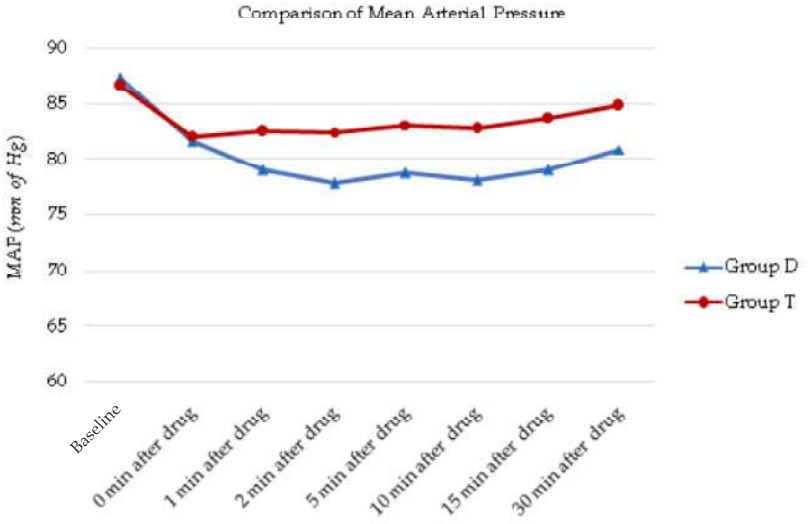

Figure 3: Line diagram showing comparison of diastolic blood pressure in study groups

those following tramadol, clinically significant bradycardia and hypotension requiring intervention was observed only in a minority of the patients, (Graph 2 and Graph 3).

Sedation with dexmedetomidine provided additional comfort to the patients and all patients could be woken up easily with verbal command or with light glabellar tap. These findings corroborate with those of Kundra *et al*.[12]

The incidence of nausea and vomiting with tramadol in our study was 37% and 11%, respectively. The results correspond with that of other studies by Reddy and Chiruvella, Tsai and Chu; Bansal and Jain.[17,9,25] However, in the study by Shukla *et al*.,[15] the incidence of nausea was quite high (77.5%), whereas Wason *et al*. have reported the incidence of nausea as only 4%.[26] These variations could be explained by the peculiar patient characteristics in different studies.

Limitations

- Sample size was small due to a limited number of people willing to participate in the study;
- Our study was conducted on ASA-I and II class patients. Further studies on elderly and compromised cardiac function patients are

required to recommend the use of tramadol and dexmedetomidine for post spinal anesthesia shivering in high risk patients.

- In our study, we used 1 *mg/kg* tramadol and 1 *μg/kg* dexmedetomidine. More studies of different dose ranges of dexmedetomidine and tramadol need to be conducted to define the ideal anti-shivering dose.

Conclusion

Both dexmedetomidine (1 *μg/kg*) and tramadol (1 *mg/kg*) are effective in treating patients with post-spinal anesthesia shivering. However, dexmedetomidine is more effective as time taken for complete cessation of shivering is shorter with dexmedetomidine as compared to tramadol and incidence of recurrence of shivering is also lower. Furthermore, dexmedetomidine does not cause adverse effects like nausea and vomiting as are seen with tramadol. Sedation caused by dexmedetomidine provides additional comfort to the patient.

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