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SCIENTIFIC ARTICLE

A prospective, randomized, double-blinded control study on comparison of tramadol, clonidine and dexmedetomidine for post spinal anesthesia shivering



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Clonidine;
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Tramadol

Abstract

Introduction: Shivering, a common intraoperative problem under spinal anesthesia increases the oxygen consumption considerably and is uncomfortable and distressing to the patient, anesthesiologist as well as surgeon. The present study was designed to explore the effectiveness of tramadol, clonidine and dexmedetomidine in the treatment of post spinal anesthesia shivering and to look for their adverse effects.

Methods: This prospective, randomized, double blinded control study was done on 90 patients who developed shivering under spinal anesthesia. They were randomly allocated into three groups with Group T receiving tramadol 1 mg.kg^{-1} , Group C getting clonidine 1 mcg.kg^{-1} and Group D patients receiving dexmedetomidine 0.5 mcg.kg^{-1} . The time taken to control shivering, recurrence rate, hemodynamic variables, sedation score and adverse effects were observed.

Results: Dexmedetomidine was faster in the control of shivering in 5.7 ± 0.79 minutes (min) whereas tramadol took 6.76 ± 0.93 min and clonidine was slower with 9.43 ± 0.93 min. The recurrence rate was much lower in the dexmedetomidine group with 3.3% than for clonidine (10%) and tramadol (23.3%) group. The sedation achieved with dexmedetomidine was better than clonidine and tramadol. The tramadol group had more cases of vomiting (four) and dexmedetomidine group had six cases of hypotension and two cases of bradycardia. Two of the clonidine patients encountered bradycardia and hypotension.

Conclusion: Dexmedetomidine is better than tramadol and clonidine in the control of shivering because of its faster onset and less recurrence rate. Though complications are encountered in the dexmedetomidine group, they are treatable.

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PALAVRAS-CHAVE

Clonidina;
Dexmedetomidina;
Hipotermia;
Tremor;
Raquiianestesia;
Tramadol

Estudo prospectivo randômico, duplo-cego e controlado comparando tramadol, clonidina e dexmedetomidina para tremores pós-raquiianestesia**Resumo**

Introdução: O tremor, problema comum no período intraoperatório sob raquiianestesia, aumenta consideravelmente o consumo de oxigênio, além de ser desconfortável e angustiante para o paciente, o anestesiologista e o cirurgião. O presente estudo foi concebido para explorar a eficácia de tramadol, clonidina e dexmedetomidina no tratamento de tremores pós-raquiianestesia e observar seus efeitos adversos.

Métodos: Este estudo prospectivo, randômico, controlado e duplo-cego foi realizado com 90 pacientes que desenvolveram tremores sob raquiianestesia. Os pacientes foram randomicamente alocados em três grupos para receber 1 mg.kg⁻¹ de tramadol (Grupo T), 1 mcg.kg⁻¹ de clonidina (Grupo C) e 0,5 mcg.kg⁻¹ de dexmedetomidina (Grupo D). O tempo necessário para controlar os tremores, a taxa de recorrência, as variáveis hemodinâmicas, os níveis de sedação e os efeitos adversos foram registrados.

Resultados: Dexmedetomidina foi mais rápida para controlar os tremores, com tempo de 5,7 ± 0,79 minutos (min); o tempo de tramadol foi de 6,76 ± 0,93 min; clonidina foi mais lenta, com tempo de 9,43 ± 0,93 min. A taxa de recorrência foi muito menor no grupo dexmedetomidina (3,3%) que nos grupos clonidina (10%) e tramadol (23,3%). A sedação obtida com dexmedetomidina foi melhor que a obtida com clonidina e tramadol. O grupo tramadol teve mais casos de vômito (quatro); o grupo dexmedetomidina teve seis casos de hipotensão e dois casos de bradicardia. Dois pacientes do grupo clonidina apresentaram bradicardia e hipotensão.

Conclusão: Dexmedetomidina foi melhor que tramadol e clonidina para o controle de tremores devido ao seu início de ação mais rápido e taxa de recorrência mais baixa. Embora complicações tenham sido observadas no grupo dexmedetomidina, elas foram tratáveis.

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Introduction

Shivering is an oscillatory, involuntary mechanical muscular activity and a natural protective mechanism to the reduction of body temperature. The body tries to raise the metabolic heat generation to restore homeostasis by shivering.¹ The core temperature in humans is normally maintained within a tight range of 36.5–37.5°C which is known as the interthreshold range or thermo neutral zone. Thermoregulatory responses like vasoconstriction and shivering are activated when core temperature falls below the normal range.² The spinal α -motor neurons and their axons mediate the neurological mechanism of shivering with center at the preoptic nucleus of the anterior hypothalamus.³

The incidence of shivering following spinal anesthesia is not exactly known for references quoting as high as 30–60%.⁴ The shivering increases heat production up to 600% and oxygen consumption is tripled. This can lead to several metabolic abnormalities like hypoxemia, hypercarbia, lactic acidosis, increased intraocular and intracranial pressure.^{5,6} In patients with coronary artery disease, shivering can further compromise myocardial function.⁷

Several pharmacologic and nonpharmacologic strategies are available for the treatment of shivering with no consensus on the gold standard therapy.⁸ The nonpharmacologic strategies include blankets, warming intravenous fluids and use of external warmer. Several drugs have been studied for the prophylaxis as well as treatment of shivering. This includes pethidine, tramadol, nefopam, ketamine,

dexmedetomidine, granisetron, physostigmine, clonidine, magnesium sulphate, dexamethasone, and urapidil.⁹ But unfortunately, no single drug has been found to be effective and without any adverse effects. Pethidine was long considered as the agent of choice to control shivering but many institutions are nowadays avoiding pethidine because of its adverse effects.⁸

The objective of this prospective, randomized, double-blinded control study is to compare the efficacy, recurrence rate, hemodynamics and complications of tramadol, clonidine and dexmedetomidine in the treatment of shivering following spinal anesthesia.

Materials and methods

The study was performed after obtaining institutional ethical committee approval and written, informed consent from patients in a tertiary medical college hospital. Patients in the age group of 18–70, American Society of Anesthesiologists (ASA) 1 and 2 and scheduled to undergo elective surgeries under spinal anesthesia and developing shivering were included in the study. Patients with ASA 3 and above, cardiac, liver and renal diseases, allergic to any of the study drugs or patient refusal and pregnant patients were excluded from the study. The patients who developed shivering under spinal anesthesia were randomly divided into three groups with 30 patients in each group. Group T patients received tramadol 1 mg.kg⁻¹, Group C

had clonidine 1 mcg.kg^{-1} and Group D received dexmedetomidine 0.5 mcg.kg^{-1} . The group allotment was decided by the computer generated random envelope method. The first anesthiologist opens the envelope and adds the study drug in a 100 mL normal saline and hands it to the second anesthiologist who is blinded to the study drug. He administers the drug over 10 min and monitors the patient.

Standard monitoring of Electrocardiogram, noninvasive blood pressure, oxygen saturation and axillary temperature were done on all patients. The operating room temperature was maintained at 22°C for all the surgeries. No external warming devices were used and fluids were administered at room temperature to all patients. The patients received spinal anesthesia with 25 gauge Quincke spinal needle to achieve a level of at least T10 depending on the type of surgery. Patients who developed shivering were included in the study. The shivering intensity was graded on a scale of 1–4 as per Wrench. Grade 1 was patients having one or more of the following: piloerection, peripheral vasoconstriction, peripheral cyanosis, but without visible muscle activity. Grade 2 includes visible muscle activity confined to one muscle group. Grade 3 was visible muscle activity in more than one muscle group. Grade 4 was taken as gross muscle activity involving the whole body. The patients were included in the study when they develop shivering with at least a Grade of 2.

The hemodynamic monitoring was continued after the administration of study drugs. The time taken to control shivering, recurrence and adverse effects like nausea, vomiting, dry mouth and sedation score were observed. The sedation score proposed by Filos et al. was followed. Grade 1 was taken as awake and alert patient. Grade 2 being drowsy patient responding to verbal stimuli. Grade 3 was taken as drowsy but arousable to physical stimuli and Grade 4 was

unarousable patient. The monitoring was continued for two hours after the administration of spinal anesthesia.

Statistical analysis was performed using a standard statistical program, The Statistical Package for Social Sciences version 17.0 software (IBM Corporation, Armonk, NY, USA). Demographic data were analyzed using One-way Analysis of Variance (ANOVA) test. The time taken to control shivering, heart rate and blood pressure were expressed as mean \pm standard deviation and statistical analysis was done by One-way ANOVA with posttest. The level for all analyses was set at $p=0.05$ with a p -value less than 0.05 were considered statistically significant and p -value less than 0.01 were considered extremely significant. If p -value was significant then Students' t -test was done between two groups to determine the statistical significance. The sedation score, recurrence rate and adverse effects were analyzed using two way ANOVA test for block design.

Results

Three hundred and twelve patients were recruited into the study and a Consolidated Standards of Reporting Trials flow diagram depicting the passage of participants through the trial has been provided in Fig. 1.¹⁰

The two groups were comparable with respect to the demographic profile and there was no statistically significant difference as shown in Table 1. There were also no significant baseline variations in hemodynamic parameters and mean axillary temperature. The time taken to control shivering was significantly faster in dexmedetomidine ($5.76 \pm 1.14 \text{ min}$) group than tramadol ($6.72 \pm 1.27 \text{ min}$) and clonidine ($9.48 \pm 0.95 \text{ min}$) group. The p -value was <0.0001 which was highly significant by One way Analysis of variance

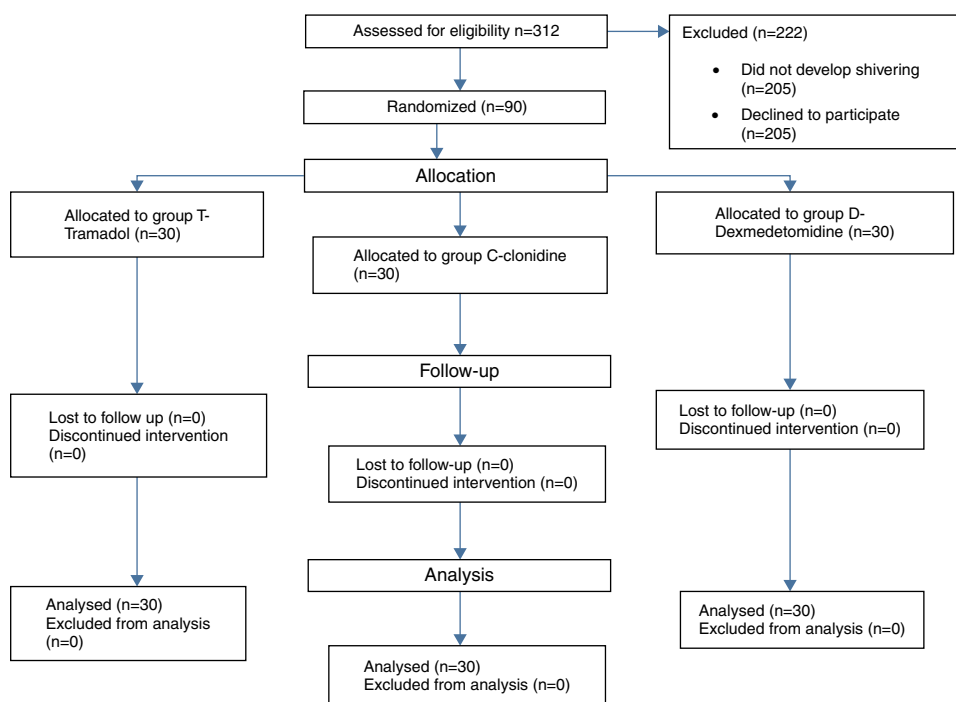


Figure 1 CONSORT flow chart (CONSORT, Consolidated Standards of Reporting Trials).

Table 1 Demographic characteristics.

Patient characteristics	Group T	Group C	Group D	p-Value
Age (years)	37.42 ± 6.27	36.84 ± 5.87	35.78 ± 6.76	0.596 ^a
Body weight (kg)	66.65 ± 7.46	68.73 ± 8.34	67.34 ± 7.62	0.578 ^a
Height (cm)	166.34 ± 10.45	164.42 ± 11.23	162.72 ± 10.72	0.433 ^a
ASA physical status 1/2	14/16	15/15	12/18	1.001 ^a
Gender (M/F)	12/18	13/17	12/18	0.667 ^a
Mean duration of anesthesia (min)	62.43 ± 3.78	64.54 ± 4.42	63.32 ± 4.43	0.157 ^a
Mean axillary temperature (°C)	36.88 ± 0.55	36.77 ± 0.14	36.83 ± 0.24	0.097 ^a

All values are mean ± SD or numbers. Statistical analysis by One-way Analysis of Variance (ANOVA) with posttest.

^a Not significant.

(ANOVA) test. There were significant variations in the heart rate after the administration of the study drug between the three groups and is depicted in Table 2. There was reduction in heart rate in dexmedetomidine and clonidine group with no significant changes in the tramadol group. The changes in systolic and diastolic pressure after drug administration were given in Tables 3 and 4. There was reduction in systolic and diastolic blood pressure more so in the dexmedetomidine group than clonidine and tramadol groups.

The sedation score was significantly higher in the dexmedetomidine group with 70% of patients having a score of 2 and 23.3% patients developing a score of 3 (Fig. 2). However, no patient in any group developed a score of 4. The sedation achieved during the treatment of shivering was

beneficial for these patients under spinal anesthesia. The recurrence rate was significantly less in the dexmedetomidine group (3.3%) and highest in the tramadol group (23.3%). The clonidine group had a recurrence rate of 10%. The shivering was not controlled in two patients in the clonidine group and one in the tramadol group and rescue drug pethidine was used for them. The incidence of vomiting was higher in the tramadol group (13.3%) than clonidine (3.3%) and dexmedetomidine group (0 patients). However two patients developed bradycardia each in the dexmedetomidine as well as clonidine group which responded well to atropine. The incidence of hypotension was significantly higher in the dexmedetomidine (20%) than clonidine (13.3%) and tramadol (6.6%) groups.

Table 2 Variations in heart rate after study drug administration.

Time (min)	Group T (beats/min)	Group C (beats/min)	Group D (beats/min)	p-Value	Intergroup comparison when $p < 0.05$
0	73.72 ± 4.68	74.9 ± 5.21	74.41 ± 4.25	0.625 ^c	–
10	76.83 ± 3.78	70.42 ± 3.17	68.53 ± 2.49	<0.0001 ^b	<0.001 ^d <0.001 ^e 0.013 ^f
20	74.41 ± 5.21	71.28 ± 5.39	65.42 ± 4.95	<0.0001 ^b	0.0259 ^d <0.001 ^e <0.001 ^f
30	70.5 ± 3.94	72.39 ± 4.27	68.42 ± 4.83	0.002 ^a	0.065 ^d 0.060 ^e 0.001 ^f
40	71.31 ± 3.19	71.43 ± 3.55	69.39 ± 2.73	0.023 ^a	0.890 ^d 0.065 ^e 0.023 ^f
50	71.19 ± 4.82	72.37 ± 4.57	70.33 ± 5.03	0.258 ^c	–
60	72.1 ± 4.04	72.32 ± 4.44	71.49 ± 3.89	0.734 ^c	–

Statistical analysis by One-way ANOVA with posttest. All values are mean ± SD.

^a Significant.

^b Highly significant.

^c Not significant.

^d Group T vs. Group C.

^e Group T vs. Group D.

^f Group C vs. Group D.

Table 3 Variations in systolic blood pressure after study drug administration.

Time (min)	Group T (mmHg)	Group C (mmHg)	Group D (mmHg)	p-Value	Intergroup comparison when ($p < 0.05$)
0	108.32 ± 9.56	107.54 ± 8.72	108.47 ± 9.52	0.916 ^c	–
10	104.65 ± 7.41	102.53 ± 9.58	98.68 ± 10.72	0.047 ^a	0.3417 ^d 0.0149 ^e 0.1478 ^f
20	106.53 ± 8.63	98.8 ± 7.91	94.88 ± 8.48	<0.0001 ^b	0.0006 ^d 0.0001 ^e 0.0692 ^f
30	104.59 ± 8.29	103.5 ± 9.48	99.39 ± 9.48	0.069 ^c	–
40	104.89 ± 10.42	103.6 ± 6.92	103.77 ± 9.38	0.834 ^c	–
50	102.66 ± 6.83	104.7 ± 8.99	102.79 ± 10.29	0.582 ^c	–
60	103.58 ± 9.82	102.69 ± 10.69	102.29 ± 8.73	0.872 ^c	–

Statistical analysis by One-way ANOVA with posttest. All values are mean ± SD.

^a Significant.

^b Highly significant.

^c Not significant.

^d Group T vs. Group C.

^e Group T vs. Group D.

^f Group C vs. Group D.

Discussion

The shivering is a protective response occurring as part of a centrally mediated thermoregulatory defense mechanism to hypothermia.¹¹ The shivering is a frequent complication under regional anesthesia occurring either as a result of a decrease in core body temperature or misinformation from receptors.¹² The shivering under anesthesia not only increases the oxygen consumption but also causes tachycardia, hypertension and interferes with the monitoring of pulse oximeter, electrocardiogram and blood pressure. In spite of the availability of numerous drugs to treat shivering, there is

no consensus drug that effectively controls shivering without any side effects.

The α_2 agonists commonly used to treat shivering acts by decreasing the central thermo sensitivity by suppressing the neuronal conductance.¹³ They decrease the release of nor-adrenaline from the axonal terminals in the hypothalamus.¹⁴ There is high density of α_2 receptors in the hypothalamus and these receptors activation leads to hypothermia by reducing the generation of heat by metabolic activity.¹⁵ Dexmedetomidine has an advantage in its ability to produce dose dependent sedation and can be used as an anesthetic adjuvant.^{16,17} Tramadol acts by inhibiting the neuronal

Table 4 Variations in diastolic blood pressure after study drug administration.

Time (min)	Group T (mmHg)	Group C (mmHg)	Group D (mmHg)	p-Value	Intergroup comparison when ($p < 0.05$)
0	75.63 ± 4.82	74.75 ± 5.86	76.33 ± 4.47	0.486 ^a	–
10	72.43 ± 6.18	70.83 ± 7.84	68.43 ± 6.38	0.081 ^a	–
20	71.88 ± 3.91	68.6 ± 5.28	66.18 ± 6.35	0.0003 ^b	0.0083 ^c 0.0001 ^d 0.1139 ^e
30	70.96 ± 5.37	69.27 ± 6.39	67.88 ± 4.72	0.103 ^a	–
40	72.82 ± 6.49	71.15 ± 4.92	70.19 ± 6.48	0.235 ^a	–
50	74.7 ± 3.73	73.47 ± 6.20	72.55 ± 5.62	0.292 ^a	–
60	76.85 ± 4.72	77.28 ± 3.72	75.66 ± 7.36	0.498 ^a	–

Statistical analysis by One-way ANOVA with post-test. All values are mean ± SD.

^a Not significant.

^b Highly significant.

^c Group T vs. Group C.

^d Group T vs. Group D.

^e Group C vs. Group D.

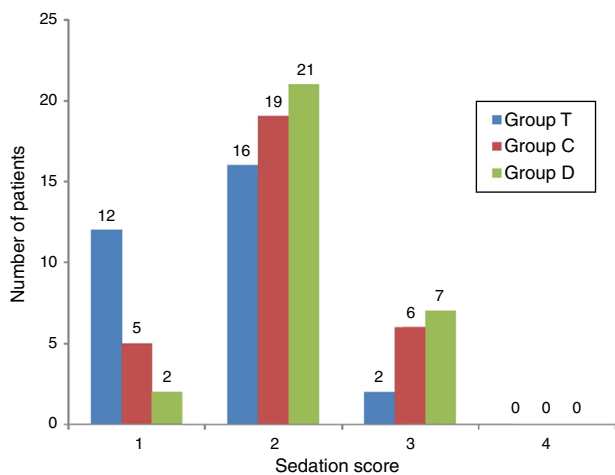


Figure 2 Sedation score.

uptake of serotonin and noradrenaline and enhances the hydroxytryptamine secretion.¹⁸

The shivering was controlled faster in the dexmedetomidine group and it took a longer time in the clonidine group than tramadol group. Mittal et al. performed a study on the comparison of dexmedetomidine and tramadol for post spinal anesthesia shivering. They concluded that dexmedetomidine in a dose of 0.5 mcg.kg^{-1} had a faster onset to control shivering in $2.52 \pm 0.44 \text{ min}$.¹⁹ Bansal did a comparative study on control of shivering with clonidine, butorphanol and tramadol under spinal anesthesia. They reported that tramadol was more effective than clonidine in suppressing shivering.²⁰ Usta et al. conducted a study on dexmedetomidine infusion for the prevention of shivering during spinal anesthesia. They observed that dexmedetomidine infusion of $0.4 \text{ mcg.kg}^{-1}.\text{h}^{-1}$ was effective in preventing shivering and providing sedation for minor surgical procedures.²¹

The sedation achieved was better in the dexmedetomidine group than clonidine and tramadol group. Since the surgery was done under spinal anesthesia, sedation achieved was beneficial for these patients. However, none of the patients became unarousable in all the three groups. Bozgeyik et al. performed a study on the effects of preemptive tramadol and dexmedetomidine on shivering during arthroscopy. They observed that in addition to its effectiveness in preventing shivering, dexmedetomidine was superior in increasing the level of sedation to prevent anxiety without side effects.²²

Only one patient in the dexmedetomidine group developed recurrence of shivering whereas seven patients in the tramadol group and three patients in the clonidine group encountered recurrence which was treated with pethidine. Mittal et al. reported the shivering recurrence was doubled in the tramadol group than dexmedetomidine group.¹⁹ Bansal et al. reported a recurrence of 26% with clonidine and 30% with tramadol.²⁰ These studies also confirm that recurrence of shivering was much lower in the dexmedetomidine group than tramadol and clonidine.

The vomiting was observed more frequently in the tramadol group with four patients and one patient in the clonidine group. The bradycardia was observed in two

patients each in clonidine and dexmedetomidine. However, the incidence of hypotension was observed more frequently in the dexmedetomidine group. But hypotension and bradycardia responded well to treatment. Kim et al. reported hypotension in 6.6% and bradycardia in 16.6% of patients with dexmedetomidine 1 mcg.kg^{-1} .²³ Mittal et al. did not have any hypotension with dexmedetomidine 0.5 mcg.kg^{-1} but vomiting was observed 20% in tramadol group.¹⁹

The limitations of our study include a relatively smaller size sample. Though dexmedetomidine was effective in the treatment of shivering, side effects were reported with it which was treatable. A larger study is needed to report an ideal drug for shivering. Secondly, we did not measure the core temperature but used the axillary temperature in all patients. Thirdly, the incidence of shivering would have been less if we have used external warming devices for all patients.

We conclude that dexmedetomidine is more effective than tramadol and clonidine in the treatment of shivering because of its faster onset, lesser recurrence rate, and better sedation. The complications reported with dexmedetomidine were easily treatable and did not have much clinical impact. Tramadol is better than clonidine in treating shivering but has more incidence of unpleasant vomiting.

Conflicts of interest

The authors declare no conflicts of interest.

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