Original Article

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Comparison between Dexmedetomidine, Ketamine and Tramadol for Prevention of Perioperative Shivering under Spinal Anaesthesia: A Randomised Clinical Trial

Anaesthesia Section

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ABSTRACT

Introduction: Perioperative shivering after spinal anaesthesia is a common complication. Ketamine and tramadol are routinely used to prevent perioperative spinal shivering. Ketamine has the side-effect of delirium while tramadol causes nausea and vomiting. Dexmedetomidine an alpha2 agonist is superior to tramadol and ketamine in view of better central vasoconstrictor tone regulation and less sympathetic activity.

Aim: To compare the efficacy, effect on haemodynamics, and any adverse effects of tramadol, ketamine and dexmedetomidine when used prophylactically to prevent perioperative shivering after spinal anaesthesia.

Materials and Methods: This, randomised, clinical study recruited adult patients aged 18-65 years, of American Society of Anaesthesiologists (ASA) I and II, of both genders undergoing surgery under spinal anaesthesia between February 2018 and August 2018. A total of 120 patients were assigned to four groups: T, D, K, and N, to receive Tramadol 0.5 mg/kg or Dexmedetomidine 0.5 µg/kg or Ketamine 0.25 mg/kg or normal saline 5 mL, respectively. Each study drug was diluted to 5 mL using normal saline and administered as a slow intravenous (i.v.) bolus injection five minutes before spinal anaesthesia. Patients received subarachnoid block in L3-4 or L4-5 space in sitting position with 0.5% hyperbaric bupivacaine 15 mg. Patients were monitored for shivering, (using a four-point scale), level of consciousness, heart rate, SpO_2, respiratory rate, non invasive blood pressure, nausea and vomiting, at intervals of every five minutes for the first 30 minutes and every 15 minutes for the remaining observation period.

Results: Dexmedetomidine (n=0) offered lower incidence of shivering prevention after spinal anaesthesia than ketamine (n=2, 6.6%), tramadol (n=10,33%) and normal saline groups (n=11, 36.6%). Dexmedetomidine also provided the advantages of maintaining haemodynamics, respiratory rate, and consciousness, similar to ketamine or tramadol (p-value >0.05).

Conclusion: Dexmedetomidine is superior to ketamine and tramadol for the prevention of shivering after spinal anaesthesia.

Keywords: Alpha2 agonist, Hypothermia, Postoperative N-methyl-d-aspartate receptor antagonist

INTRODUCTION

Shivering, a common postspinal anaesthesia occurrence, is defined as an involuntary, repetitive activity of skeletal muscles. The incidence of perioperative shivering is relatively high, approximately 40-70% after neuraxial anaesthesia [1,2]. It increases oxygen consumption and carbon dioxide production, induces lactic acidosis and causes patient dissatisfaction and discomfort [3]. Shivering may also increase intraocular and intracranial pressure, increase wound pain, delay wound healing, and delay discharge from postanaesthetic care [4]. It also has the disadvantage of interfering with the monitoring of blood pressure, electrocardiogram and oxygen saturation. When the preoptic region of the hypothalamus is cooled shivering is elicited as a physiological response to raise metabolic heat production through muscle contraction [5]. The aetiology of intra/postoperative shivering is multifactorial and includes temperature loss, increased sympathetic tone, pain, and systemic release of pyrogens.

Spinal anaesthesia reduces the tonic vasoconstriction leading to impairment of thermoregulatory system and decrease in shivering threshold. Spinal anaesthesia with sensory loss extending upto T6 level may cause sympathetic paralysis resulting in extensive vasodilatation. Shivering can be controlled by non pharmacological and pharmacological methods. Non pharmacological means include covering the skin (e.g., surgical drapes, blankets or plastic bags) and forced-air warming using Baer-Hugger, i.v. fluid and blood warmers should be used to minimise the incidence of shivering while administering the i.v. fluids, blood and blood products during the operation. The irrigating solutions should be used after warming them closer to human body temperature for irrigating the wound during surgery. Also, heat loss and thus shivering can be minimised by using warm, humidified oxygen via nasal prongs throughout the surgery. As several neurotransmitter pathways of opioids, alpha2 adrenergic, serotonergic and anticholinergic receptors are involved, various pharmacologic agents have been used for prophylaxis and treatment of postspinal shivering like opioids like fentanyl, Tramadol [6-8], meperidine [6] anticholinergic: physostigmine, N-methyl-d-aspartate (NMDA) receptor antagonist ketamine [5] and α2 agonists clonidine [7] and Dexmedetomidine [8-11].

Tramadol is a favoured and commonly used drug for postspinal anaesthesia shivering. It inhibits serotonin and noradrenaline uptake in the spinal cord and stimulates the secretion of hydroxyl-tryptamine, thus modulating the human temperature regulation centre. Ketamine, another agent, has gained popularity during the last decade. It is a competitive NMDA receptor antagonist that acts in thermoregulation by inhibiting norepinephrine uptake into postganglionic sympathetic nerve endings [12]. Dexmedetomidine, a recent drug used for sedation decreases the shivering threshold by reducing the vasoconstriction [13]. Dexmedetomidine has lower incidence of nausea and vomiting, than tramadol and also provides better sedation than ketamine [13]. As perioperative shivering can be very harmful to the patients, the focus should be on prevention

rather than treatment. Various studies have been conducted on tramadol and ketamine. But only a few trials are available on recent drug dexmedetomidine comparing with either tramadol or ketamine. Dexmedetomidine controls shivering better with lesser nausea than tramadol [14]. Dexmedetomidine offers lower shivering with higher sedation than ketamine [15]. As dexmedtomidine offers the dual advantage of lower incidence of nausea than tramadol and more sedation than ketamine, a trial necessiating the head-to-head comparison of dexmedetomidine with both these drugs is essential.

Hence, this clinical study was planned to compare the efficacy, effect on haemodynamics, and any adverse effects of tramadol, ketamine, and dexmedetomidine when used prophylactically to prevent perioperative shivering after spinal anaesthesia. The primary objective was the efficacy in reducing shivering. The secondary objectives were impact on the haemodynamics, level of sedation, and adverse effects.

MATERIALS AND METHODS

A randomised, clinical study was conducted between February 2018 and August 2018 in Nizams Institute of Medical Sciences, Hyderabad, Telangana, India. The study was started following approval of the Institutional Ethics Committee (IEC) (number: EC/NIEC/NIMS/2046/2017). Registration was obtained with the clinical trial registry of India (http://ctri. nic.in/Clinical trials), CTRI/2020/12/029892.

Inclusion criteria: A total of 120 adults between 18-65 years, ASA I and II, of both sexes undergoing lower limb or lower abdominal surgeries under spinal anaesthesia who gave informed consent were included in the study.

Exclusion criteria: Patient refusal, ASA III and IV, drug allergy, compromised cardiorespiratory functions, renal or hepatic disease, thyroid, and psychiatric disorders, severe diabetes or autonomic neuropathies, known history of substance or alcohol abuse, pregnant patients, obese (body mass index >30 kg/m^2), contradictions to spinal anaesthesia, patients having Visual Analogue Scale (VAS) >6 intraoperatively were offered general anaesthesia and were excluded from the study.

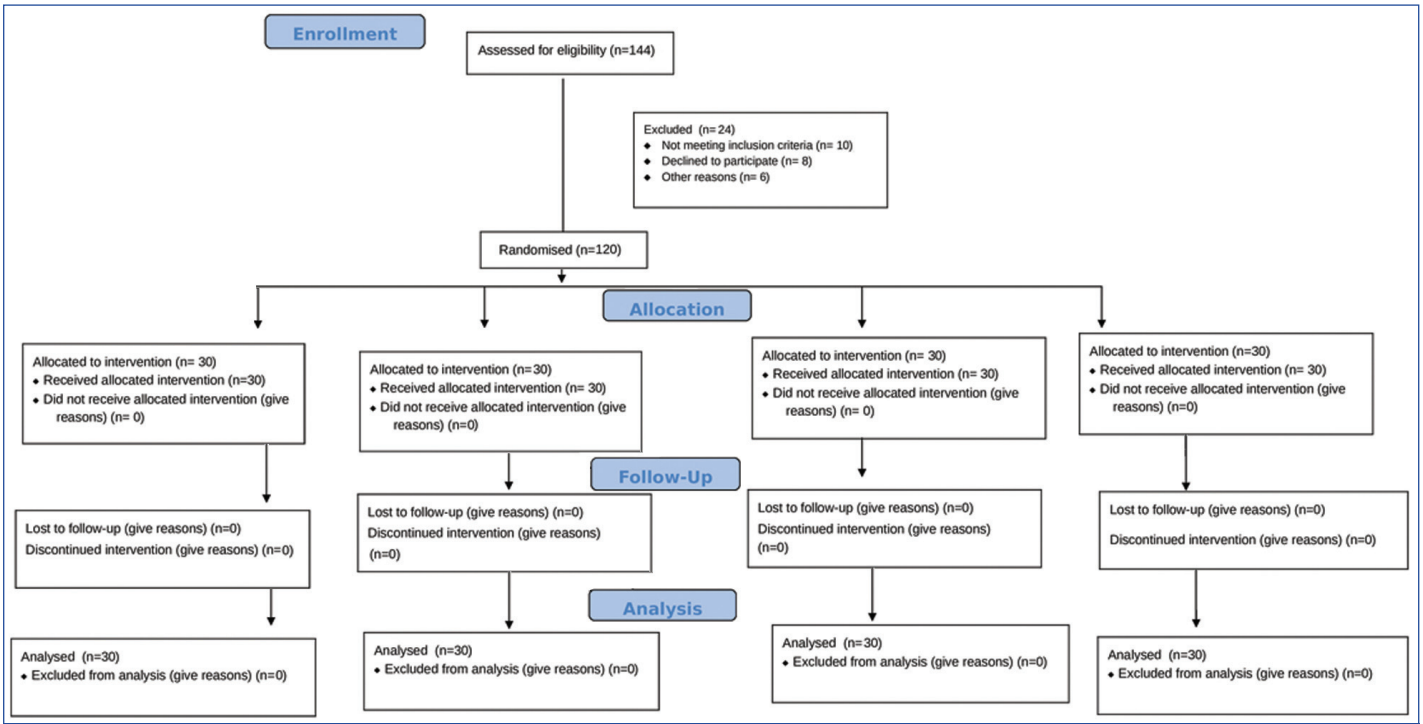
Sample size calculation: The sample size was estimated based on a pilot study. At 80% of the statistical test with five patients in each group, using the formula:

$$\text{Sample size } n=\frac{2(Z\alpha+Z1-\beta)^2\times\sigma^2}{(m1-m2)^2}$$

The mean±SD of incidence of shivering for the first sample were 70.1±2.3. And that for the second sample were 68±2.1. Hence minimum number of samples required in each group was 21. However, considering attrition 30 members in each group were considered.

Study Procedure

Subjects were divided into four groups of 30 each [Table/Fig-1], using simple randomisation, according to the computer-generated table of random numbers-group T-IV tramadol 0.5 mg/kg, Group D-IV dexmedetomidine 0.5 µg/kg, group K-IV ketamine 0.25 mg/kg and group N-normal saline was given. All patients received a standardised anaesthetic protocol after a detailed preanaesthetic examination. This included overnight fasting and premedication with Tab Alprazolam 0.25 mg and Tab Ranitidine 150 mg on the night before surgery. On arrival at the operation theatre, intravenous access with an 18G i.v. cannula was secured. In this study, all Operation Theatres (OTs) were maintained at an ambient temperature of 22°-25°C, and all fluids and drugs were kept at room temperature during the surgery. Preloading was done with Ringer's Lactate solution at room temperature at 10 mL/kg rate before giving spinal anaesthesia. In the operating room, standard monitoring was done for level of consciousness, electrocardiogram, SpO_2, respiratory rate, non invasive blood pressure:(systole and diastole), shivering, nausea and vomiting at intervals of every 5 minutes for the first 30 minutes and every 15 minutes for the rest of the observation period. A standard blanket was used to cover the patients, chest and upper limbs. One of the three study drugs alone with normal saline was given as a slow i.v. bolus injection five minutes prior to spinal anaesthesia. The drugs were diluted to a volume of 5 mL in a 5 mL syringe. Under sterile aseptic conditions, a subarachnoid block was performed using a 25G cutting, quincke spinal needle in L3-L4 or L4-L5 space in sitting position. About 15 mg of 0.5% hyperbaric bupivacaine was administered at a rate of 0.2 mL/sec in the subarachnoid space (after clear aspiration of CSF). Pinprick method at the midaxillary line was used to assess the level of spinal block. The patients were prepared for surgery as the block level of T10 was achieved.



[Table/Fig-1]: CONSORT 2010 flowdiagram.

All patients were observed for shivering and graded with a four-point scale [16]: 0-No shivering, 1-piloerection or peripheral vasoconstriction but no visible shivering, 2-muscular activity in only one muscle group, 3-muscular activity in more than one muscle group, 4-whole body shivering. The level of sedation was assessed by a four-point ordinal scale [17]: 0-Awake and alert, 1-drowsy and responsive to verbal stimuli, 2-drowsy and responsive to physical stimuli, 3-unarousable. Perioperative nausea and vomiting were assessed using the four-point ordinal scale: 0-no nausea/vomiting, 1-nausea, 2-retching, 3 -vomiting [17]. Heart rate, SpO_2, respiratory rate, non invasive blood pressure, were recorded at intervals of every five minutes for the first 30 minutes and every 15 minutes for the remaining observation period.

STATISTICAL ANALYSIS

Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) version 21.0. Continuous data were calculated with the Analysis of Variance (ANOVA) test and represented as mean±SD. Both categorical data and ordinal data were mentioned as frequency and percentages. Categorical data (shivering, sedation, nausea and vomiting) were calculated with the Chi-square test.

RESULTS

A total of 120 patients who underwent surgery under spinal anaesthesia, were studied. The four groups were comparable in terms of demographic data as there were no significant differences in terms of age, weight, sex and ASA grade [Table/Fig-2]. Dexmedetomidine had a statistically lower incidence of shivering than ketamine and tramadol [Table/Fig-3]. The heart rates, on comparison within all the groups, were not found to be statistically significant (p-value >0.05) from the baseline values upto 90 minutes [Table/Fig-4].

Parameters	Group D	Group K	Group T	Group N	p-value
Age (years) (Mean±SD)	38±15.81	39.97±14.24	45.8±15.23	40.37±4.41	0.41
Weight (Kgs) (Mean±SD)	62.7±11.16	64.11±2.32	65.7±.8.91	65.3±10.28	0.89
Sex (M: F) (n)	20:10	18:12	23:7	20:10	0.58
ASA :1/2 (n)	19/11	22/8	20/10	22/8	0.78

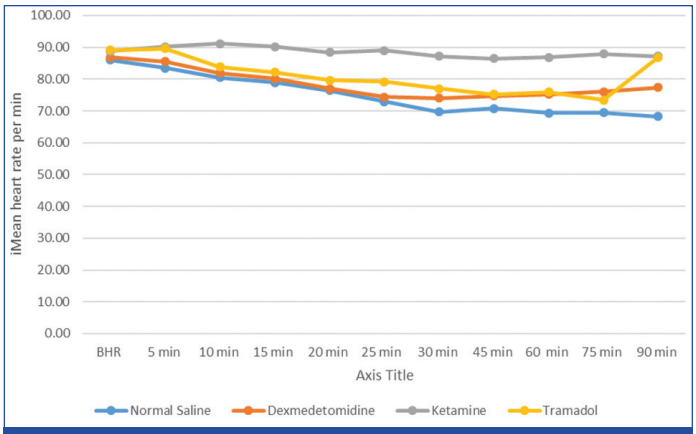
[Table/Fig-2]: Demographic profile comparison.
Group D: Dexmedetomidine, Group K: Ketamine group, Group T: Tramadol, Group N: Normal saline, n: Number of patients

Groups	No. of patients according to shivering grade (n)					Total no. of patients (n)	p-value
	0	1	2	3	4		
Normal saline (n)	19	4	4	3	0	11 (36.6%)	0.027
Dexmedetomidine (n)	30	0	0	0	0	0	
Ketamine (n)	28	1	0	1	0	2 (6.6%)	
Tramadol (n)	20	4	3	2	1	10 (33%)	

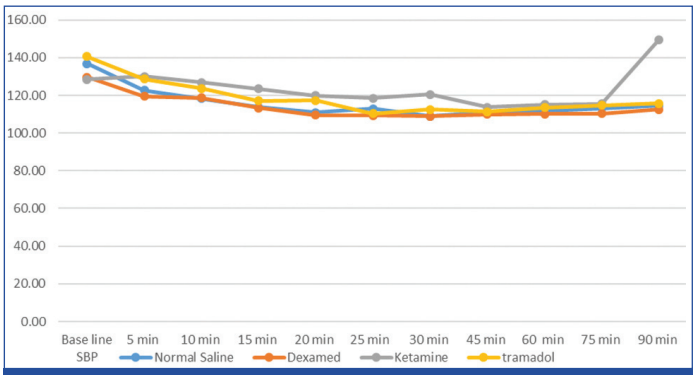
[Table/Fig-3]: Grades of shivering comparison.
n: Number of patients

The SBP on comparison within dexmedetomidine and tramadol groups were found to be statistically insignificant (p-value >0.05) upto 90 minutes from the baseline values, but it was significantly more in the ketamine group at 30 minutes [Table/Fig-5]. The DBP on comparison among all groups showed a similar variation (p-value >0.05) from the baseline values upto 90 minutes [Table/Fig-6].

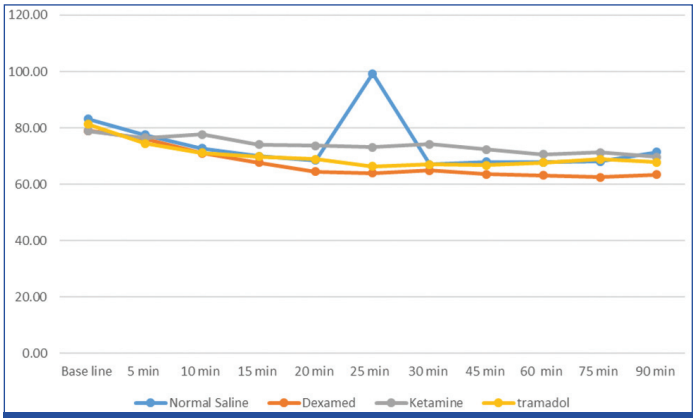
The respiratory rate on comparison between the dexmedetomidine and tramadol groups was found to be similar (p-value >0.05) up to 90 mins, but respiratory rate was highest for ketamine from 15-75 min and the difference was significant [Table/Fig-7]. Regarding SpO_2, a similar variation was noted among all the four groups (p-value >0.05) upto 90 minutes [Table/Fig-8]. The level of consciousness, nausea, and vomiting were similar among the four groups (p-value >0.05) upto 90 minutes [Table/Fig-9].



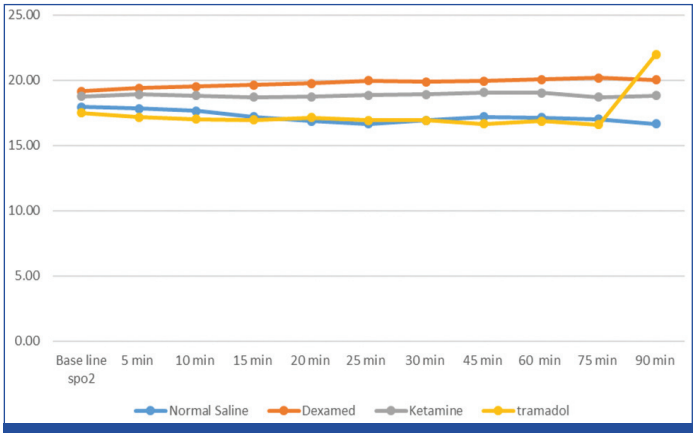
[Table/Fig-4]: Heart rate comparison.
(p>0.05 from the baseline values up to 90 minutes)



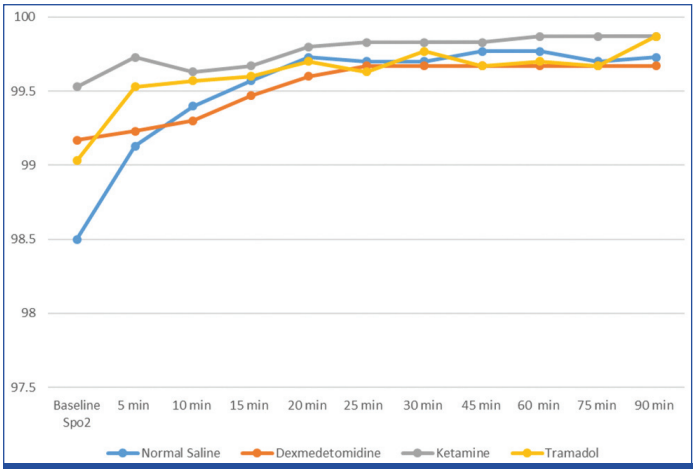
[Table/Fig-5]: Systolic Blood Pressure (SBP) comparison.
(p>0.05 up to 90 min from the baseline values, but at 30min significantly highest for the Ketamine group)



[Table/Fig-6]: Diastolic Blood Pressure (DBP) comparison.
(p>0.05 from the baseline values up to 90 minutes)



[Table/Fig-7]: Respiratory rate comparison.



[Table/Fig-8]: SpO_2 changes comparison.
(p>0.05 up to 90 minutes)

Variables	Group D	Group K	Group T	Group N	p-value
Level of sedation (Grade: 0/1) (n)	26/4	25/5	27/3	30/0	0.159
Nausea and vomiting (n)	0	2	4	0	0.221

[Table/Fig-9]: Level of sedation, nausea and vomiting.
Group D: Dexmedetomidine, Group K: Ketamine group, Group T: Tramadol, Group N: Normal saline, n: Number of patients

DISCUSSION

Shivering is commonly experienced by the patients undergoing abdominal and lower limb surgeries under neuraxial blockade of spinal and epidural anaesthesia. The different pharmacological agents of opioids, ketamine, alpha 2 adrenergic agonists that are available are of limited use in view of side-effects. This randomised clinical trial was conducted to compare the efficacy in the prevention of shivering. Dexmedetomidine was found to be superior over tramadol and ketamine. The study by Bozgeyik S et al., on dexmedetomidine (0.5 µg/kg and Tramadol (2 mg/kg), concluded that both effectively prevent postspinal shivering, but dexmedetomidine had caused more sedation. Regarding shivering, results of the present study were comparable with dexmedetomidine being better than tramadol, but there was no incidence of sedation with dexmedetomidine [18].

Wang J et al., performed a meta-analysis of randomised controlled trials to compare dexmedetomidine with tramadol. They concluded that dexmedetomidine controls shivering better than tramadol, while also decreasing the incidences of recurrence [14]. This was similar to the present study. Similarly, in the trial by Houssein M and Ibrahim I, dexmedetomidine group patients had reduced postspinal anaesthesia shivering but more profound sedation (grade 4) than ketamine (0.25 mg/kg) [15]. Sahi S et al., conducted a trial between dexmedetomidine (1 µg/kg), clonidine (2 µg/kg), tramadol (1 mg/kg) along with normal saline. All three drugs prevented postspinal shivering, but tramadol had significantly less nausea and shivering [19]. However, in the present study dexmedetomidine was more effective than tramadol in prevention of shivering. Hidayah MN et al., conducted a study between, ketamine (0.5 mg/kg), and tramadol (1 mg/kg) on postspinal anaesthesia shivering [20]. The ketamine group had significant lower shivering (8%) than tramadol (16%) and control (24%) group, but significantly higher mean arterial blood pressure and heart rate at 5 and 15 minutes and behavioural changes and side-effects. Although in the present study, low doses of ketamine (0.25 mg/kg) and tramadol (0.5 mg/kg) were administered, the incidence of shivering was comparable with the observations of Hidayah MN et al., i.e. it was 6% in ketamine, 33% in tramadol, 33% in normal saline and 0% in dexmedetomidine. Patients had higher mean haemodynamic parameters in the ketamine group compared to other groups but without causing any side-effects.

Limitation(s)

As this study was conducted in a single centre this might not be applicable to the general population.

CONCLUSION(S)

Present study concluded that dexmedetomidine is superior than ketamine and tramadol in the prevention of shivering after spinal anaesthesia (p=0.027). Dexmedetomidine also offers the advantage of maintaining in stable haemodynamics, respiratory rate and consciousness with low adverse effects of nausea and vomiting similar to other drugs.

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