Original Research Article

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Comparison of prophylactic dexmedetomidine and ketamine for the control of shivering under spinal anaesthesia

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ABSTRACT

Background: Shivering is a common problem during neuraxial block. Thermoregulatory control gets compromised by neyraxial block and as a result the incidence of shivering can go up to 56.7%. Aim of the current investigation was to evaluate the effectiveness of prophylactic use of intravenous dexmedetomidine and ketamine for the control of shivering and to note any side-effects of the drugs used during subarachnoid block.

Methods: This randomised single blind study was conducted in 151 ASA grade I and II patients. SAB was performed with 3.0mL (15 mg) of 0.5% bupivacaine heavy in all patients. Patients were randomly allocated into two groups of 75 and 76each to receive dexmedetomidine (0.5 μ g/kg) in group D and ketamine (0.5 mg/kg) in group K respectively. Temperature and hemodynamic parameters were recorded at every 15mins interval. Shivering was graded from 0 to 4 according to Tsai and Chu and if grade 3 shivering occurred, the study was stopped and pethidine 25 mg was given intravenously as rescue drug.

Results: 2.67% of patients in group D had shivering whereas 38.16% patients in group K experienced shivering at the 5th minute after spinal anaesthesia and it was statistically significant. However the difference in the incidence of shivering was not statistically significant between the two groups after the initial 5 minutes till the end of surgery.

Conclusions: The prophylactic use of dexmedetomidine reduced incidences of shivering more effectively as compared to prophylactic use of ketamine. None of the drugs caused any untoward side effects.

Keywords: Dexmedetomidine, Ketamine, Neuraxial block, Shivering

INTRODUCTION

Post-anaesthetic shivering (PAS) is a common complication following general and regional anaesthesia. Various studies reported the incidence of shivering to be between 5% and 65% in patients recovering from general anaesthesia and 40 and 60% in patients recovering from regional anaesthesia. Shivering is an involuntary, repetitive activity of skeletal muscles which occurs as a physiological response to combat hypothermia. Shivering increases oxygen requirement, basal metabolic rate, lactic

acidosis and carbon dioxide production. Core body temperature is maintained within very narrow levels by the hypothalamus. This is known as the interthreshold range, sweating and vasodilation at one extreme and vasoconstriction and shivering at the other.

Anaesthetic agents inhibit central thermoregulation by interfering with these hypothalamic reflex responses. Both general and regional anaesthesia increase the interthreshold range, though by different mechanisms. Spinal and epidural anaesthetics, like general anaesthetics,

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lead to hypothermia by causing vasodilation and internal redistribution of heat. The accompanying thermoregulatory impairment from regional anaesthetics that allows continued heat loss is likely due to altered perception by the hypothalamus of temperature in the anaesthetised dermatomes rather than a central drug effect, as with general anaesthetics. Various pharmacological agents have been evaluated for their efficacy in preventing and treating peri and postoperative shivering. However, no drug treatment has been defined as ideal. Studies have shown that several agents may be efficacious in treatment of PAS, including meperidine, clonidine, ondansetron, granisetron, midazolam, sufentanil, alfentanil, tramadol, physostigmine, and nalbuphine.^{1,3} Among meperidine is the most widely used.

In recent years, several studies have evaluated the efficacy of ketamine for prevention of post anaesthesia shivering. Ketamine is an inexpensive, widely available general anesthetic agent that produces analgesia and amnesia, with or without loss of consciousness, by antagonizing the Nmethyl-D-aspartate (NMDA) receptor in the brain.4 The NMDA receptor is also thought to play a role in the transmission of thermal signals to the brain and spinal cord. Ketamine differs from other anaesthetic agents as it produces a significant analgesic effect whilst rarely causing cardiovascular or respiratory depression.⁵ Recent studies have shown that ketamine may prevent PAS at doses of 0.75 mg/kg or less, which decreases the likelihood of adverse effects like cardiovascular stimulation, delirium and other psychological effect produced at higher doses of ketamine. Though the role of ketamine in prevention of shivering is not fully understood, it appears that it is likely to affect thermoregulation through more than one mechanism. Ketamine decreases core-to-peripheral redistribution of heat by preventing the vasodilation that occurs with other anaesthetic agents. In addition, it is hypothesized that ketamine may prevent shivering by interfering with thermoregulatory control mechanisms in thebrain. Due to its unique properties, low cost, and wide availability, ketamine should be evaluated for its efficacy in preventing shivering post anaesthesia.

Dexmedetomidine, a parenterala-2 selective agonist has sedative properties as well as reduces the shivering threshold. Few studies which have been conducted on this drug have inferred that it is an effective drug without any major adverse effects and provides good haemodynamic stability.⁷⁻¹²

Therefore current study was planned to do a comparative study to evaluate the efficacy of a parenteral α -2 selective agonist dexmedetomidine and an NMDA antagonist ketamine for prevention of shivering in patients undergoing lower abdominal or lower limb surgery under spinal anaesthesia.

METHODS

A randomised single blind comparative study was done at IPGMER hospital, Kolkata form January 2015 to August 2016 on 151 patients of ASA grade 1 and 2, belonging to either sex, aged between 18 and 65 years, undergoing lower abdominal or lower limb surgery under spinal anaesthesia.

Patients suffering from neuromuscular disease, hyperthyroidism, history of cardiopulmonary disease, psychological disease, refusal to participate or temperature >38°C or <36.5°Cwere excluded from the study. The patients were randomly allocated into two groups; group D (n=75) received dexmedetomidine 0.5 μ /kg intravenously diluted to 4 ml with NS and group K (n=76) received ketamine 0.5 mg/kg intravenously diluted to 4 ml with NS.

Following a detailed pre-anaesthetic checkup along with relevant investigations, patients were brought to the operation theatre (OT) and standard monitors attached. Baseline parameters like heart rate, mean arterial pressure, Spo2, core and surface temperature were recorded. All the patients were pre-loaded with Ringer lactate 10 ml/kg before giving neuraxial block. The study drug and intravenous fluids were pre-heated to 37°C before administering them to the patient. The temperature of the OT was maintained at 24±1°C for all the patients.

Neuraxial anaesthesia was instituted at either L3-4 or L4-5 interspaces using 3.0 ml of hyperbaric bupivacaine 0.5% using a 25 gauge quincke's spinal needle. The study drug was administered to the patients after subarchnoid block. During the intraoperative period pulse rate, non-invasive blood pressure (NIBP), oxygen saturation, temperature (core and surface) were assessed at 15 minutes intervals. The core temperature was measured by a nasopharyngeal thermometer and surface temperature by an axillary thermometer. Shivering was graded using a scale validated by Tsaiand Chu.⁵ According to the scale grade 0=no shivering, grade 1=piloerection butno visible shivering, grade 2=muscular activity in only one group, grade 3=muscular activity in more than one muscle group but not generalized and grade 4=shivering involving the whole body.

During surgery, the shivering score was recorded at 5-min intervals till the end of surgery. The prophylaxis was regarded as ineffective if the patients exhibited grade 3 shivering any time during the study and then intravenous pethidine 25 mg was administered as a rescue drug. Hallucinations, bradycardia and sedation were also recorded. Hypotension was defined as a decrease in mean blood pressure (MBP) of more than 20% from the baseline. Hypotension was treated with i.v. bolus dose of mephentermine 3 mg and a further i.v. infusion of Ringer lactate. If patients had nausea and vomiting, i.v. metoclopramide10 mg was administered. Hallucination as a side effect was defined as a false sensory experience

where the patients reported that they saw, heard, smelled, tasted or felt something that was nonexistent. The degree of sedation was assessed by Ramsay sedation score: 1=patient anxious, agitated or restless, 2=patient cooperative, oriented, tranquil, 3=patient responding only to verbal commands, 4=patient with brisk response to light glabellar tap or loud auditory stimulus, 5=patient with sluggish response to light glabellar tap or loud auditory stimulus and 6= patient with no response to light glabellar tap or loud auditory stimulus. Written informed consent from all the patients were also taken before including them in the study.

Sample size was determined on the basis of incidence of shivering as the primary outcome measured assuming that the incidence of shivering in group K (ketamine) would be 20% on basis of earlier study. It was calculated that 75 subjects would be required per group in order to detect a difference 15% between the two drugs with 80% power and 5% probability of type 1 error. Testing would be 2 sided. Statistical evaluation was done with nMaster 2.0 software (department of biostatistics, Christian medical college, Vellore).

RESULTS

One fifty one patients, aged between 18-65 years of ASA grade I and II, scheduled to undergo infraumbilical and lower limb surgeries under spinal anaesthesia were randomly divided into two groups. Group D received dexmedetomidine (0.5 μ g/kg) and group K received ketamine (0.5 μ g/kg). Comparison between various parameters was done. Demographic data (age, sex, bodyweight) was comparable in both the groups (Table 1).

Table 1: Demographic data.

Parameter	Group	K	p value
Sex (%)	M (50.67) F (49.33)	M (47.37) F (52.63)	0.746
Age (years)	34.49±10.787	36.03±11.638	0.403
Weight (kg)	59.05±7.725	58.92±7.897	0.917

Though the baseline heart rate was comparable in both the groups; in the intra-operative period group D had a lower heart rate trend compared to group K which was statistically significant (Figure 1). The mean arterial pressure variation in both the groups was comparable (Figure 2). The temperature in both the groups were comparable except in the 15th min where Group K had lower temperature than Group D and this was statistically significant (p<0.05) (Figure 3). Patients belonging to Group K had higher incidence of shivering as compared to group D which was statistically highly significant (p<0.001) (Table 2). The incidence of shivering in group

D was much less than that of group K as depicted in (Figure 4).

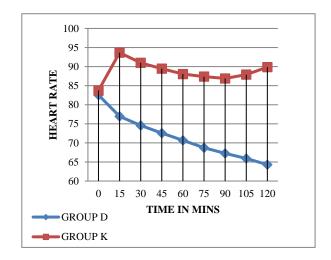


Figure 1: Trend of heart rate in both groups.

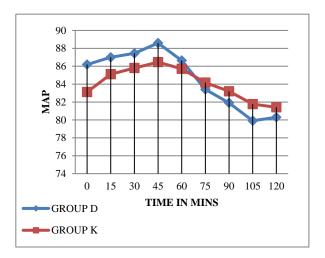


Figure 2: Trend of mean arterial pressure in both groups.

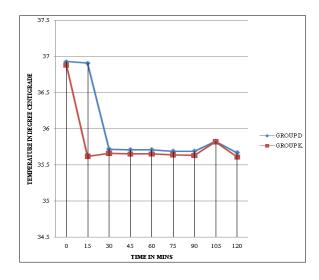


Figure 3: Trend of temperature in both groups.

Table 2: Incidence of shivering in both groups.

Data analyzed	Yes	No	p value
Group D (n=75)	5	70	_
Group K (n=76)	35	41	< 0.001
Total	40	111	_

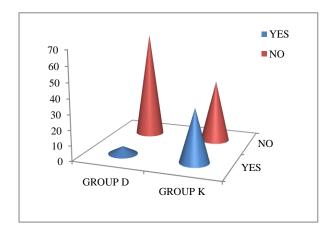


Figure 4: Incidence of shivering in both groups.

Patients belonging to group K showed greater incidence of grade 3 and grade 4 shivering in comparison to group D (Table 3). Patients in group K required rescue drug whereas none required rescue drug in group D, and the result was statistically significant (Table 4). Patients belonging to group D had more incidences of bradycardia and sedation which was statistically significant (Table 5).

DISCUSSION

Peri-operative shivering is a distressing experience for the patient. The exact mechanism of shivering during spinal anaesthesia has not been fully recognized. The commonly recognised theories include impairment of central thermoregulation, internal redistribution of body heat, and heat loss to the environment. Age, level of sensory block, temperature of the operation theatre and IV solutions are the potential risk factors for hypothermia in spinal anaesthesia. In this study, the ambient temperature of operation theatres (OTs) was maintained at 23-25°C, and all fluids and drugs were stored at room temperature during the surgery. For reduction of any confounding bias; ages, gender, duration of anaesthesia and surgery have also been matched.

Table 3: Comparison of different grades of shivering.

Time (minutes)	Group D (n=75) Shivering grades			Group K (n=76) Shivering grades				p value			
	0	1	2	3	4	0	1	2	3	4	·
5	73	1	1	0	0	47	6	6	10	7	< 0.001
10	72	1	2	0	0	73	0	2	1	0	0.572
15	75	0	0	0	0	74	0	2	0	0	1.000
25	75	0	0	0	0	75	1	0	0	0	1.000
50	75	0	0	0	0	75	1	0	0	0	1.000

Table 4: Patients receiving treatment for shivering.

Data analyzed	Yes	No	p value
Group D (n=75)	0	75	0.0007
Group K (n=76)	11	65	0.0007

Table 5: Incidence of side effects in the 2 groups.

Side effects	Group	Inc	idenc	p value		
Duadmandia	D	10		0.005		
Bradycardia	K	1				
		Gra	de			
Sedation		1	2	3	0.002	
	D	53	18	4		
	K	70	6	0		

The neurotransmitter pathways involved in shivering are multiple and involve opioids, a2 adrenergic, serotonergic, and anticholinergic receptors. The drugs commonly used in the treatment of shivering areopioids (pethidine,

nalbuphine, or tramadol), ketanserin, propofol, doxapram, clonidine, ketamineand nefopam. However, there are

unwanted adverse effects such as hypotension, hypertension, sedation, respiratory depression, nausea and vomiting . Hence, the hunt for an ideal anti-shivering agent is still continuing.

Alpha-2 adrenergic agonists are widely becoming very popular nowadays in anaesthesia and critical care settings. Dexmedetomidine is an α2 adrenoceptor agonist, with antihypertensive, sedative, analgesic, and anti-shivering properties. The anti-shivering effects of alpha adrenoceptor agonists are mediated by binding to α2 receptors that mediate vasoconstriction and the antishivering effect. In addition, it has hypothalamic thermoregulatory effects. Dexmedetomidine comparably reduces the vasoconstriction and shivering thresholds, thus suggesting that it acts on the central thermoregulatory system rather than preventing shivering peripherally. Is It has been successfully used as an adjunct to local

anaesthetics in spinal anaesthesia and peripheral nerve blockade, for the sedation of mechanically ventilated patients in the intensive care unit, as well as supplementation of post-operative analgesia. ^{13,16} The role of dexmedetomidine in the treatment of shivering has been evaluated in a few studies. ^{9,17,18} It may be a good choice in critical care setup because of its anti-shivering effect and sedation.

Ketamine, an NMDA receptor antagonist, also has a role in thermoregulation at various levels. It increases blood pressure, heart rate and cardiac output. The mechanism of action of ketamine is by direct sympathetic stimulation and inhibition of norepinephrine uptake into the postganglionic sympathetic nerve endings, and thus it may decrease core to peripheral redistribution of heat.¹⁹ Ketamine may cause side-effects such as hallucination. Sagir et al found ketamine 0.5 mg/kg i.v. to be effective in controlling shivering under neuraxial blockade. 19 Dal et al witnessed significant results with ketamine 0.5 mg/kg i.v. to prevent shivering under general anaesthesia.20 Gangopadhyay et al concluded that ketamine 0.5 mg/kg i.v. was effective in preventing shivering under spinal anaesthesia.2 Honarmand in his study, with patients undergoing orthopaedic surgery under subarachnoid anaesthesia concluded that prophylactic use of ketamine 0.25 mg/kg and midazolam 37.5 mcg/kg i.v. was more effective than ketamine 0.5 mg/kg i.v. or midazolam 75 mcg/kg i.v. in preventing shivering developed during regional anaesthesia.²¹ Kose et al reported that prophylactic ketamine 0.25mg/kg was as effective as ketamine 0.5 mg/kg in preventing shivering in patients undergoing cesarean delivery.²²

Bajwa et al carried out their study on patients who underwent general anesthesia for laparoscopic surgical procedures and found incidence of shivering was 42.5% in placebo group which was significant as compared to the dexmedetomidine group. Kim enrolled patients scheduled for elective laparoscopic total hysterectomy. The incidence of shivering was significantly lower in group D 0.75 (dexmedetomidine 0.75 $\mu g/kg$) and D1.0 (dexmedetomidine 1.0 $\mu g/kg$) than in group SS (0.9% normal saline). 10

Bozgeyik et al compared 100 mg tramadol (group T) vs. $0.5 \,\mu\text{g/kg}$ dexmedetomidine (group D) vs. saline (group P) in patients undergoing elective arthroscopic surgery with SA. In group T and D, shivering scores were significantly lower when compared with group P.¹¹ Mittal et al conducted a study in patients scheduled for various surgical procedures under spinal anaesthesia using dexmedetomidine $0.5 \,\mu\text{g/kg}$ or tramadol $0.5 \,\text{mg/kg}$. They found that dexmedetomidine fared much better than tramadol to reduce time taken for stopping of shivering.¹²

Limitations

Limitations of current study were; small sample size, single blind study, post operative temperature recordings

were not taken. Control group was not taken, so the measure of absolute efficacy of a particular drug could not be done. In this study two drugs were compared who belong to two completely different groups with completely different mechanism of action. There was no way to find out the equivalent dose of one drug in respect to the other one. Therefore further studies are required to assess the lowest effective dose of the study drugs to control shivering under spinal anaesthesia.

CONCLUSION

Prophylactic dexmedetomidine and ketamine both reduced the incidence of shivering without any major adverse effects. However, in the initial perioperative period dexmedetomidine significantly reduced the shivering associated with spinal anaesthesia in comparison to ketamine.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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