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Intravenous Low Dose Ketamine Injection versus Dexmedetomidine Infusion for Prevention of Intraoperative Shivering During Spinal Anesthesia: A Prospective Randomized Controlled Study

Mostafa Mansour Houssein* and Ibrahim Mohamed Ibrahim

Department of anesthesia and intensive care, Ain Shams University, Egypt

***Corresponding Author:** Mostafa Mansour Houssein, Department of anesthesia and intensive care, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

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Abstract

Background: Shivering is considered one of the most common adverse effects occurring during spinal anesthesia. Besides causing patient discomfort, shivering also interferes with patient monitoring and increases tissue oxygen demand. The present study was conducted to compare the effectiveness of *iv* low dose Ketamine (0.25 mg/kg) and dexmedetomidine *iv* infusion in prevention of shivering during spinal anesthesia.

Materials and Methods: Sixty patients of both sexes were included in this prospective randomized controlled study. Patients were divided randomly into two group's thirty patients each. Group K (30 patients) received low dose Ketamine (0.25 mg/kg) and group D (30 patients) received Dexmedetomidine infusion. The primary outcome measures of this study were intraoperative shivering. Secondary outcome measures were hemodynamic changes, sedation scores and postoperative side effects.

Results: Patients in group D had a lower incidence of post spinal anesthesia shivering compared to patients in group K. 13.33% of group K patients reached grade 3 shivering in comparison to only 3.33% of patients in group D 10 min. after onset of spinal anesthesia ($p = 0.031$). Deeper sedation was observed in group D patients as 36.67% of group D patients reached grade 4 sedation compared to 23.33% of patients in group K after 10 minutes ($p = 0.048$)

Conclusion: Dexmedetomidine infusion is more effective as an anti-shivering and sedating agent than low dose Ketamine injection in patients receiving spinal anesthesia.

Keywords: *Spinal anesthesia; Ketamine; Dexmedetomedine; Shivering*

Introduction

Shivering is considered one of the common complications occurring during spinal anesthesia and its incidence was reported to reach up to 56.7% [1,2]. Shivering leads to patient inconvenience and also interfere with monitoring of electrocardiogram (ECG), blood pressure (BP), and oxygen saturation. It increases oxygen consumption, carbon dioxide production and may lead to lactic acidosis. It also increases intracranial and intraocular pressures [3,4].

The normal human core temperature usually ranges from 36.5ºC to 37.5ºC [5]. Thermoregulation (which is a part of homeostatic mechanism) is done at the level of the anterior hypothalamus. The anterior hypothalamus compares the peripheral inputs with a threshold value, or the set-point. if the temperature was lower than this set point, this will activate certain reflexes to warm the body, while If the temperature was higher than this set point, this will trigger a cooling responses [6].

Both cooling and worming responses are decreased during regional anesthesia, suggesting affection in central, rather than peripheral control [7]. Impairment of centrally mediated thermoregulation by the local anesthetics is usually caused by alteration in the afferent thermal inputs from legs. All thermal inputs from the blocked regions are interrupted by regional anesthesia, which is primarily cold information. This decrease in cold information is then interpreted by the brain as relative leg warming [8].

Various methods are available to control shivering during anesthesia. These methods are either pharmacological or non-pharmacological. Pharmacological methods use drugs which have anti-shivering properties like clonidine, pethidine, nefopam, tramadol, ketanserine, doxapram, etc. This method is cost effective, simple, and easy to implement. The non-pharmacological methods using equipment to maintain normal temperature of the body are effective but expensive and lack practicality.

Recently, Ketamine and Dexmedetomidine have been tried to prevent shivering during anesthesia with good results. Ketamine (a competitive NMDA receptor antagonist) has a role in thermoregulation at various levels. NMDA receptor modulates serotonergic and nor-adrenergic neurons in locus ceruleus. It is used as anti-shivering agent in a dose of 0.25 - 0.75 mg/kg IV. But even in these doses, it causes side effects (i.e. drowsiness, delirium, hallucination) [9,10].

Dexmedetomidine is a highly selective α 2 - adrenergic receptor agonist with potent effects on the central nervous system [11,12]. Although Dexmedetomidine is among several pharmacological agents used for the treatment of shivering, its effects as anti-shivering during central neuroaxial blockade have not been evaluated to date.

Aim of the study: The aim is to compare between intravenous low dose of Ketamine and intravenous infusion of dexmedetomidine for prevention of intraoperative shivering during spinal anesthesia.

Materials and Methods

This prospective randomized controlled study was carried out at Ain - Shams University Hospital after obtaining the approval of the local ethical committee. The study design was assigned as parallel with active control group. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12614001246673). Date of registration was 27/11/2014, registered by Mostafa Mansour Houssein.

Sixty patients of both sexes between 20 to 50 years old undergoing elective lower abdominal surgery and elective orthopedic lower limb surgery were included in the study. Patients selected were American Society of Anesthesiologists (ASA) I and II physical status. After approval of local ethics committee, all subjects gave written consents to participate. Patients with thyroid disease, parkinson´s disease, dysautonomia, Raynaud´s syndrome, cardiopulmonary disease, a need for blood transfusion during surgery, a history of allergy to the agents to be used, an initial core temperature > 37.5ºC or < 36.5ºC, a known history of alcohol use, use of sedative - hypnotic agents, use of vasodilators, or having contraindications to spinal anesthesia were excluded from the study. All operation theatres in which the operations were performed maintained at constant humidity 70% and an ambient temperature of around 23ºC. Irrigation and i.v. fluids were administered at room temperature and given without in line warming. No other warming device was used. A core temperature below 36ºC was considered hypothermia. Before performing spinal anesthesia, each patient received 10 ml/kg of lactated Ringer's solution. Before beginning of spinal anesthesia, standard monitoring of heart rate, non-invasive blood pressure (NIBP), oxygen saturation (SpO2) and body temperature (axillary) were recorded and then every 10 minutes. Subarachnoid anesthesia was instituted at either L3/4 or L4/5 inter space with 3 ml of 0.5% hyperbaric Bupivacaine (Marcaine®, spinal heavy 0.5%, AstraZeneca) using 25 gauge Quincke's needle, and blockade up to T9 - T10 dermatome was achieved. Motor block was assessed using a modified Bromage scale (0 = no motor block, 1 = can flex knee, move foot but cannot raise leg, 2 = can move foot only, 3 = cannot move foot or knee) [13]. Sensory block was assessed by the pinprick test.

After spinal anesthesia, group K received a prophylactic low dose of Ketamine (0.25 mg/kg), while group D received a prophylaxis of Dexmedetomidine (Precedex®). Dexmedetomidine ampoule (200 µg/ml) was diluted to a volume of 50 ml (4 µg/ml). Patients received a dosed of 1 µg/kg dexmedetomidine over 10 min. by a syringe pump (perfuser compact, Braun, Germany) followed by continuous infusion of 0.4 µg/kg/h during the surgery which was stopped at the completion of surgery. Supplemental oxygen (2 L/min.) was delivered via a nasal cannula during the operation.

Grading of shivering was done which is as following: [14]

Grade 0: No shivering

Grade 1: Peripheral vasoconstriction or Piloerection or peripheral cyanosis 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 whole body.

If shivering grade was 3 or greater at 15 minutes after spinal anesthesia, the prophylaxis was considered ineffective, and 25mg Pethidine was administered by i.v. route.

Side effects like nausea, vomiting, bradycardia (< 60/min.), hypotension (> 20% decline below baseline), dizziness, and sedation were recorded.

The degree of sedation was assessed using a 5 points scale: [15]

1 = fully awake and oriented patient.

2 = Drowsy.

3 = eyes closed, arousable on command.

4 = eyes closed, arousable to physical stimuli.

5 = eyes closed, unarousable to physical stimuli.

If the patient's heart rate drops below 60 beat/min. 0.5 mg atropine was administered by i.v. route. If mean arterial pressure (MAP) drop more than 20% from baseline, 10 mg ephedrine via i.v. bolus is given and further i.v. infusion of lactated Ringer's solution is required. If the patients developed nausea and vomiting, 10 mg metoclopramide was administered through i.v. route. Heart rate, mean arterial pressure (MAP), temperature and oxygen saturation (SpO_2) were recorded as a baseline before the start of spinal anesthesia then recorded every 10 minutes during intra-operative period till the end of operation.

The primary outcome measures were intraoperative shivering score. Secondary outcome measures were hemodynamic parameters (heart rate, mean arterial pressure, oxygen saturation and temperature) measured at baseline then every 10 min., sedation scores and postoperative side effects (e.g. nausea, vomiting, and dizziness).

Statistical Analysis

Sample size was calculated using PASS 11. Based on a pilot study, it was calculated that a sample size of 24 patients per group will achieve 80% power to detect a 10% decrease in the occurrence in shivering in the dexmedetomidine group compared to ketamine group. The significance level of the test was targeted at 0.0500. Thirty patients per group were included to replace any dropouts.

Methods of Randomization

a. Randomization of patients was done using a computerized program (SPSS).

b. Sealed envelopes were numbered according to the randomization tables.

c. Packing, sealing and numbering of the envelop was performed by a neutral medical personnel (Under the supervision of doctors from the Department of Anesthesiology).

d. The number of cases included in this study was simple randomly allocated into two groups (30 in each group).

Data were analyzed using Statistical Program for Social Science (SPSS) version 18.0. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done

a. Paired sample t-test of significance was used when comparing between related samples.

b. Chi-square (X2) test of significance was used in order to compare proportions between two qualitative parameters.

c. Probability (P-value): P-value ≤ 0.05 was considered significant. P-value 0.01 was considered as highly significant.

Results

Comparison of the demographic data (age, sex, weight, height, ASA physical status, duration of surgery, type of surgery) showed no statistically significant difference between the two groups. (P > 0.05) (Table 1)

		Group (K)		Group (D)		t-test	
		Mean	± SD	Mean	± SD	t/*x^2	p-value
Age (years)		33.86	12.04	35.22	9.36	0.339	0.692
Body Weight (Kg)		71.92	17.22	74.22	12.17	0.488	0.628
Height (cm)		169.31	11.96	174.53	14.93	1.220	0.229
Duration of Surgery (min)		48.83	13.22	51.12	9.63	0.626	0.535
		No.	%	No.	%	-	-
Gender	Male	17	56.67	14	46.67	*0.267	0.066
	Female	13	43.33	16	53.33	-	-
ASA	I	8	26.67	11	36.67	*0.308	0.578
	II	22	73.33	19	63.33	-	-
Type of surgery	Lower Abdominal surgery	12	40.00	11	36.67	*0.163	0.892
	Lower limp Orthopedic surgery	18	60.00	19	63.33	-	-

Table 1: *Characteristics of patients in the two groups.*

Data are expressed as frequency and percentage or mean (SD).

**x^2 - Chi-square test; t - independent - sample t - test; p - value > 0.05 NS.*

This table shows no statistically significant difference between the two groups as regards patient's characteristics.

These tables (Tables 2,3,4) show that there are statistically significance differences between the two groups as regard HR, MAP and temperature. Heart rate and mean arterial pressure (MAP) were lower in group D in comparison with group K especially at 50 minutes with a HR mean (SD) of 67.82 ± 6.38 bpm and MAP mean (SD) of 69.30 ± 15.86 mmHg and also at 60 minutes with a HR mean (SD) of 67.12 ± 9.83 bpm and MAP mean (SD) of 65.30 ± 14.86 mmHg.

Body temperature was lower in group K than group D beginning from first 10 minutes with mean ± SD of 36.60 ± 0.20 at 10 minutes. There was no statistically significant difference between the two groups regarding oxygen saturation (SpO_2). (P > 0.05)

Hemodynamic		Base line		After 10 min.		After 20 min.		After 30 min.		After 40 min.		After 50 min.		After 60 min.	
		Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
HR	Group (K)	70.53	7.11	77.12*	9.26	79.42*	10.56	81.72†	9.46	84.02†	8.36	84.32†	7.26	84.44†	6.16
	Group (D)	70.23	9.42	73.11	13.60	72.68	21.83	71.72	12.62	69.42	5.55	67.82	6.38	67.12	9.83
	p-value	**0.936**		**0.456**		**0.391**		**0.060**		**< 0.001**		**< 0.001**		**< 0.001**	

Table 2: *Follow up of HR in the two groups.*

**p - Value < 0.05 vs. Group D significant.*

†p - Value < 0.01 vs. Group D highly significant.

Hemodynamic		Base line		After 10 min.		After 20 min.		After 30 min.		After 40 min.		After 50 min.		After 60 min.	
		Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
MAP	Group (K)	90.43	8.32	94.83*	22.92	97.33†	19.92	101.73†	17.52	103.33†	14.82	104.73†	17.82	104.33†	14.82
	Group (D)	90.31	7.91	84.30	13.86	81.30	15.86	77.30	17.86	73.30	16.86	69.30	15.86	65.30	14.86
	p-value	**0.971**		**0.229**		**0.062**		**0.006**		**<0.001**		**<0.001**		**<0.001**	

Table 3: *Follow up of MAP in the two groups.*

**p - value < 0.05 vs. Group D significant.*

†p - value < 0.01 vs. Group D highly significant.

Hemodynamic		Base Line		After 10 min.		After 20 min.		After 30 min.		After 40 min.		After 50 min.		After 60 min.	
		Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
SPO_2	Group (K)	96.10	2.89	96.21	2.20	97.31	3.20	98.41	1.20	99.21	2.20	98.41	3.20	97.31	3.13
	Group (D)	96.39	2.76	94.81	1.20	95.71	2.20	96.91	0.20	97.73	1.20	96.91	2.20	95.78	2.80
	p-value	**0.832**		**0.092**		**0.209**		**0.003**		**0.078**		**0.237**		**0.264**	

Table 4: *Follow up of SPO_2 in the two groups.*

Table 6 and figure 1 show the relation between the two groups as regards shivering. Shivering is considered significant when the patient reaches at least to grade 3 and after 10 minutes of spinal anesthesia. After 10 minutes, 4 patients of Ketamine group reached grade 3 shivering with a percentage of 13.33 %, while only 1 patient of Dexmedetomidine group reached grade 3 with a percentage of 3.33%. After 20 minutes, 2 patients (6.67%) in Ketamine group reached grade 3 shivering while only 1 patient (3.33%) of Dexmedetomidine group reached group 3. Grade 4 shivering was not noted in any patient in either group.

Table 6 shows that there was a statistically significant difference between the two groups as regard shivering score after 10min and after 20 min. Shivering was less in group D especially after 10 and 20 minutes.

Patients in group D were more sedated than patients in group K. After 10 minutes, 11 patients (36.67%) in group D reached grade 4 sedation while only 7 patients (23.33%) in group K reached grade 4 sedation. After 20 minutes, 12 patients (40 %) in group D reached grade 4 sedation while only 7 patients (23.33%) in group K reached grade 4 sedation. No patients in either group reached grade 5 sedation (Table 5).

Hemodynamic		**Base line**		**After 10 min.**		**After 20 min.**		**After 30 min.**		**After 40 min.**		**After 50 min.**		**After 60 min.**	
		Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Temperature	Group (K)	36.70	0.11	36.60*	0.20	36.70*	0.05	36.70*	0.08	36.70*	0.09	36.80*	0.06	36.80*	0.15
	Group (D)	36.71	0.14	36.75	0.06	36.81	0.05	36.82	0.03	36.91	0.05	37.00	0.06	37.10	0.04
	p-value	**0.861**		**0.056**		**0.041**		**0.037**		**< 0.001**		**< 0.001**		**< 0.001**	

Table 5: *Follow up of temperature in the two groups:*
**p - value < 0.05 vs. Group D significant.*
†p - value < 0.01 vs. Group D highly significant.
Data are expressed as mean (SD) for parametric data.
t - Independent - sample t – test.

Table 7 shows that there was a statistically significant difference between the two groups as regards sedation (score) after 10 min and after 20 min. Patients were more sedated in group D especially after 10 and 20 minutes.

4 patients (13.33%) in group D had postoperative dizziness in comparison with 3 patients (10%) in group K. 3 patients (10%) in group D experienced intra - operative nausea and vomiting in comparison with 2 patients (6.67%) in group K (Table 6).

Table 8 shows that, there was no statistically significant difference between the two groups as regard nausea & vomiting; and dizziness.

Discussion

The present study showed that a loading dose of dexmedetomidine of 1 µg/kg followed by continuous administration at an infusion rate of 0.4 µg/kg/hr produced potent anti-shivering effect with adequate level of sedation. However, there was a tendency for the incidence of hypotension and bradycardia compared with low dose Ketamine.

Category time		Shivering Score								Chi-Square Test	
		Group (K)				Group (D)					
		Score (0)	Score (1)	Score (2)	Score (3)	Score (0)	Score (1)	Score (2)	Score (3)	x^2	p-value
After 10 min.	No.	14	7	3	4	24	3	2	1	8.062	0.031
	%	46.67	23.33	10.00	13.33	80.00	10.00	6.67	3.33		
After 20 min.	No.	15	7	6	2	23	5	1	1	7.111	0.046
	%	50.00	23.33	20.00	6.67	76.67	16.67	3.33	3.33		
After 30 min.	No.	19	4	4	3	21	6	2	1	1.382	0.783
	%	63.3	13.3	13.3	10.0	70.0	20.0	6.7	3.3		
After 40 min.	No.	20	5	3	2	23	3	2	2	2.326	0.433
	%	66.7	16.7	10.0	6.7	76.7	10.0	6.7	6.7		
After 50 min.	No.	21	6	2	1	22	5	3	0	1.893	0.601
	%	70.0	20.0	6.7	3.3	73.3	16.7	10.0	0.0		
After 60 min.	No.	19	5	3	3	20	7	2	1	2.500	0.367
	%	63.3	16.7	10.0	10.0	66.7	23.3	6.7	3.3		

Table 6: *Shivering score in the two groups.*
Data are expressed as frequency and percentage data.
x^2- Chi-square test.

Dexmedetomidine which is an α-2 adrenoceptor agonist (it has eight times higher affinity for the α-2 adrenoceptor than clonidine), produces its sedative and anxiolytic action through binding to α-2 adrenoceptors in the locus ceruleus, resulting in decrease in the release of norepinephrine with inhibition of sympathetic activity, thus decreasing heart rate and blood pressure [16]. Hypotension and bradycardia in dexmedetomidine group is augmented by the addition of the hypotensive and bradycardic effects of spinal anesthesia after reaching maximum sensory block levels. Bradycardia with dexmedetomidine infusion was increased only in cases with a loading dose.

The motor shivering center exists near to the posterior hypothalamus which receives impulses from cold receptors. Upon activation of this shivering center by the cold impulses, it sends bilateral impulses to anterior horn cells in the spinal cord resulting in increase in the tone of the skeletal muscles all over the body. Shivering is observed when muscle tone is increased above certain level [17].

The etiology of post - spinal shivering is inadequately understood. Meperidine (Pethidine), which binds to both κ-opioid and mu receptors, is usually recommended for the treatment of postoperative shivering and the anti - shivering action of meperidine has previously been attributed to its action on κ-opioid receptors [18].

Shivering is a thermoregulatory response to cold, and can complicate both general and neuroaxial anesthesia. General anesthesia causes impairment in the thermoregulatory mechanism characterized by a decrease in cold response threshold from 0.4°C to 4°C and an increase in worm response threshold. Some of the causative factors of this type of shivering may be common to both general and neuroaxial anesthesia, but some are particular to neuroaxial anesthesia [19]. Shivering may have beneficial thermoregulatory effects, but on the other hand it places the body under increased physiological stress. This physiological stress includes increase in oxygen consumption and carbon dioxide production, and increased cardiac work. Therefore, the prevention of shivering is more important than its treatment [19].

We found that not all patients who develop shivering are hypothermic and post spinal shivering is not necessarily associated with core hypothermia. Shivering can occur in patients who are normothermic.

Our results are consistent with the study done by Elvan., *et al*. [20] who reported that dexmedetomidine infusion during surgery was effective in the prevention of post - anesthetic shivering in patients undergoing elective abdominal hysterectomy.

Another study done by Bicer and colleagues in 2006 [21] founded that the incidence of shivering was 15% with dexmedetomidine and 55% with placebo following general anesthesia. Also, Coskuner., *et al*. [22] did not observe shivering with the same dose used in our study.

Bicer., *et al*. [21] reported that intraoperative intravenous dexmedetomidine of 1.0 μg/kg reduces post anesthetic shivering with effects comparable to those of Meperidine0.5mg/kg.

Many studies were done to detect the effect of Ketamine on the incidence and severity of anesthesia related shivering. Dal., *et al*. [23] showed that ketamine 0.5 mg/kg was effective in prevention of post anesthetic shivering in patients receiving general anesthesia. Sagir., *et al*. [24] showed that 0.5 mg/kg of ketamine was also effective in prevention of shivering during spinal anesthesia. In our study, 0.25 mg/kg of ketamine was also as effective as 0.5 mg/kg of ketamine. The shivering was seen in 13.33% of group K patients who reached grade 3 shivering in comparison with only 3.33% of patients in group D 10 min. after onset of spinal anesthesia ($p = 0.031$).

Nausea and vomiting are also one of the adverse effects of dexmedetomidine and occurring more frequent than in patients receiving ketamine. However, there are some studies showing no difference of dexmedetomidine compared with placebo for nausea [20].

Conclusion

Dexmedetomidine infusion exerts a beneficial dual effect as an anti-shivering and sedating agent during spinal anesthesia without any major adverse reactions. Therefore, we concluded that dexmedetomidine infusion is a good choice and better than low dose ketamine during spinal anesthesia when shivering is considered a problem.

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