Comparison between dexmedetomidine, ketamine, or dexmedetomidine–ketamine combination for control of shivering during spinal anesthesia

Sherif S. A. Rehim, Ghada M. Aboalfadl, Alaa M. Abdelatif

Department of Anesthesia and Intensive Care, Faculty of Medicine, Assiut University, Asyut, Egypt

Correspondence to Alaa M. Abdelatif, MBBCh, Department of Anesthesia and Intensive Care, Faculty of Medicine, Assiut University, Assuit, 71111, Egypt
Tel: +20 103 394 4545;
e-mail: alaamohammed25789@gmail.com

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Background
Regional anesthesia, like general anesthesia, influences the thermoregulatory process. In this study, we aimed to compare the efficacy, hemodynamic stability, and adverse effects of dexmedetomidine (DEX), ketamine, and the combination between them when used for control of shivering that occurs during spinal anesthesia.

Patients and methods
In this double-blind study, 90 male and female patients of ASA status I and II with age 18 up to 60 years old scheduled to undergo elective lower extraperitoneal abdominal and lower limb surgery using spinal anesthesia were included. This study was done from January 2017 to July 2017.

Results
There was no significant difference in shivering control among the three groups, which was complete (when post-treatment shivering score declined to score 0) in 28 (93.3%) patients in DEX group, 27 (90%) patients in ketamine group, and 25 (83.33%) patients in combination group ($P = 0.321$), whereas incomplete (when the scores decreased but did not abolish the shivering completely) in two (6.67%) patients in DEX group, three (10%) patients in ketamine group, and five (16.67%) patients in combination group ($P = 0.234$).

Conclusion
We concluded that intravenous DEX 0.4 mcg/kg, intravenous ketamine 0.3 mg/kg, or combination between DEX 0.25 mcg/kg and ketamine 0.25 mg/kg significantly controlled the shivering that occurred during spinal anesthesia. However, DEX is superior to ketamine and the combination in prevention of shivering.

Keywords:
dexmedetomidine, ketamine, shivering, spinal anesthesia

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Introduction

Shivering is a physiological response to core hypothermia in an attempt to raise the metabolic heat production. The main causes of intraoperative and postoperative shivering are heat loss, increased sympathetic tone, pain, and systemic release of pyrogens [1].

Ketamine, a competitive NMDA receptor antagonist, has a role in thermoregulation at various levels. NMDA receptor modulates noradrenergic and serotoninergic neurons in locus coeruleus. It has been reported to inhibit postoperative shivering [2].

Dexmedetomidine (DEX), 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 [3].

Patients and methods

After ethics committee approval from Assiut University Hospital and obtaining written informed consent, 90 male and female patients of ASA status I and II with age 18 up to 60 years old scheduled to undergo elective lower extraperitoneal abdominal and lower limb surgery using spinal anesthesia were included. This study was done from January 2017 to July 2017.

Patient groups

(1) Group I (DEX group) received DE × 0.4 mcg/kg intravenously (i.v.) bolus
(2) Group II (ketamine group) received ketamine 0.3 mg/kg i.v. bolus
(3) Group III (combination group) received combination between DE × 0.25 mcg/kg and ketamine 0.25 mg/kg.

Inclusion criteria

This study included 90 patients of ASA grade I–II with age between 18 and 60 years who underwent elective

lower abdominal and lower limb surgery using spinal anesthesia for an anticipated duration of more than 60 and less than 180 min (e.g. inguinal herniorrhaphy and umbilical hernia repair) who developed shivering during intraoperative or postoperative period.

Exclusion criteria

The following were the exclusion criteria:

(1) Patient refusal
(2) Patients with a BMI more than 30 kg/m^2
(3) Initial body temperature of more than 38°C or less than 36°C
(4) Known allergies to the study drugs
(5) Contraindication to spinal anesthesia such as coagulopathy
(6) Procedures that might require administration of blood or blood products and urological endoscopic operations
(7) Patients with a history of convulsions, multiple allergies, thyroid disease, Parkinson's disease, dysautonomia, Raynaud's syndrome, hypertension, and coronary artery disease
(8) Conduction abnormalities or other cardiorespiratory or neuromuscular pathology, and middle ear pathology
(9) A known history of alcohol use
(10) Treatment with sedative, hypnotic agents, or vasodilators.

Preoperative assessment and preparation

A careful medical history

(1) General examination, including heart rate (HR), noninvasive arterial blood pressure, and arterial oxygen saturation (SaO_2)
(2) Physical examination, including chest, heart, abdomen, and other systems. Routine investigations including complete blood picture, renal function test, liver function test, blood sugar, and chest radiograph if needed.

Anesthetic technique

All patients in all groups underwent a standardized spinal anesthesia protocol. The ambient temperature was maintained at 24°C with constant humidity. Patients did not receive any premedication.

Statistical analysis

The data obtained clinically were statistically analyzed using statistical package for the social sciences for personal computers (SPSS/PC). SPSS version 20 (Armonk, NY: IBM Corp) was used. The Shapiro–Wilks test was used to determine normally distributed data. Normally distributed data were expressed as mean ± SD, and abnormally distributed data as median and interquartile range. Groups were compared by one-way analysis of variance. A probability value of less than 0.05 was regarded as statistically significant.

Results

Demographic data

These patients were equally distributed in the three groups (n = 30/group). The groups were comparable with respect to age, sex, weight, height, ASA classification, type of operation, duration of operation, duration of motor block, and duration of sensory block (Table 1).

Changes in incidence of shivering

Shivering-onset time

There was no statistically significant difference for shivering-onset time between groups, which was 8.85 ± 4.87 min in DEX group, 8.46 ± 2.66 min in ketamine group, and 8.88 ± 4.89 min in the combination group (P = 0.632; Fig. 1).

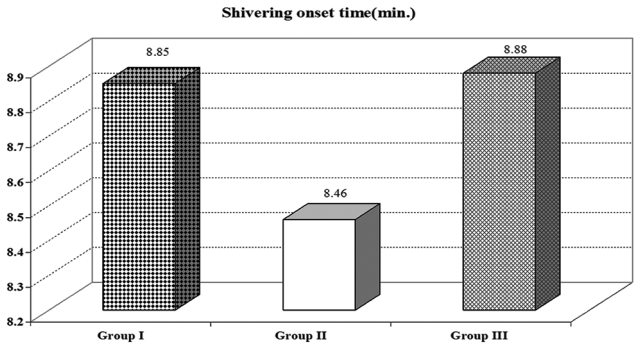
Shivering-cessation time

The time taken for complete cessation of shivering was insignificantly lower in the DEX group (35.17 ± 6.13 s) compared with ketamine (39.13 ± 8.11 s) and combination (42.15 ± 9.16) groups (P = 0.632; Fig. 2).

Shivering recurrence

Recurrence of shivering activity was significantly higher in the combination group [11 (36.7%) patients] and ketamine group [10 (33.33%) patients] compared with the DEX group [five (16.67%) patients] (P = 0.021; Fig. 3).

Figure 1

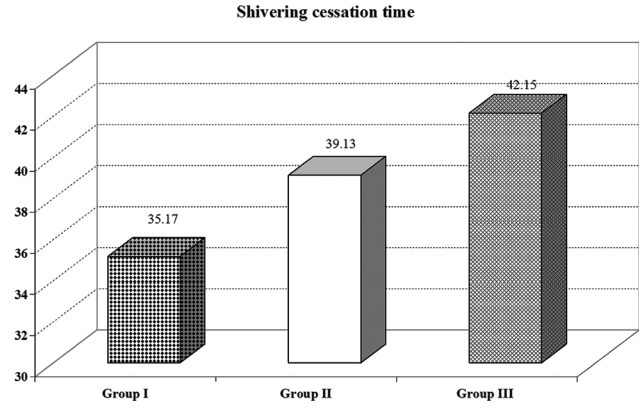


Shivering onset time.

Table 1 Demographic data, type and duration of operation, and motor and sensory block

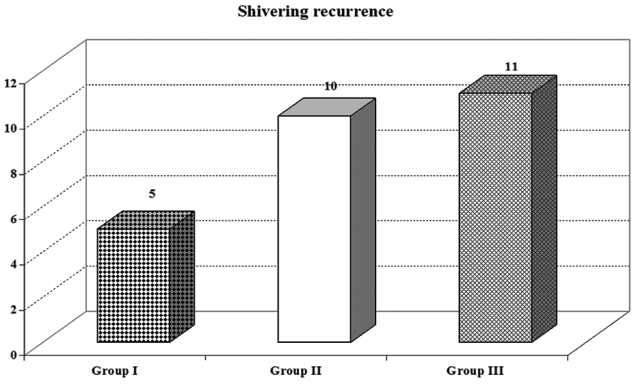
Data	Group I mixture dexmedetomidine (*n*=30)	Group II mixture ketamine (*n*=30)	Group III mixture (*n*=30)	*P*
Age (years)				
Range	19-59	20-60	18-60	0.552 (NS)
Mean±SD	30.54±8.44	31.63±11.26	31.57±8.38	
Sex [*n* (%)]				
Male	18 (60)	17 (57)	16 (53.3)	0.823 (NS)
Female	12 (40)	13 (43)	14 (46.7)	
Weight (kg)				
Range	60-80	60-80	61-80	0.986 (NS)
Mean±SD	73.0±7.00	71.87±5.06	72.83±6.11	
Height (cm)				
Range	155-180	150-180	160-180	0.123 (NS)
Mean±SD	165.4±14.55	169.5±7.86	167.5±5.98	
ASA class I/II [*n* (%)]				
I	27 (90.0)	26 (86.67)	27 (90.0)	0.885 (NS)
II	3 (10.0)	4 (13.33)	3 (10.0)	
Type of operation [*n* (%)]				
General surgery	12 (40)	11 (37)	12 (40)	0.732 (NS)
Orthopedic	12 (40)	12 (40)	11 (37)	
Urologic	6 (20)	7 (23)	7 (23)	
Duration of operation (min)				
Range	65-180	60-170	60-175	0.789 (NS)
Mean±SD	82.67±22.66	86.17±26.67	84.0±14.76	
Duration of motor block (min)				
Range	90-450	80-436	85-440	0.173 (NS)
Mean±SD	213.6±11.35	218.5±6.86	219.3±4.98	
Duration of sensory block (min)				
Range	90-280	90-280	90-280	0.531 (NS)
Mean±SD	234.5±13.35	230.6±8.86	229.8±6.95	

Figure 2



Shivering cessation time.

Figure 3



Shivering recurrence.

Control of shivering

There was no significant difference in shivering control among the three groups, which was complete (when post-treatment shivering score declined to score 0) in 28 (93.3%) patients in DEX group, in 27 (90%) patients in ketamine group, and in 25 (83.33%) patients in combination group (P = 0.321), whereas incomplete (when the scores decreased but did not abolish the shivering completely) in two (6.67%) patients in DEX group, three (10%) patients in ketamine group, and five (16.67%) patients in combination group (P = 0.234).

There was no failed control of shivering (when no change of scores was observed) in the three groups (Fig. 4).

Hemodynamic changes

Changes in systolic blood pressure

There were significant differences among the three

groups in systolic blood pressure from 0 min until 3 h after drug administration. There were significant changes in DEX and combination groups; as in the DEX group, the systolic blood pressure values significantly increased at 3 min (mean 125.1 ± 10.30), 5 min (mean 130.5 ± 8.71), and 7 min (mean 126.4 ± 9.36), and significantly decreased at 25 min (mean 112.9 ± 9.37), 30 min (mean 109.0 ± 9.24), 40 min (mean 110.6 ± 7.82), and 50 min (mean 111.7 ± 4.90) compared with the baseline (mean 118.2 ± 8.06).

In the combination group, the systolic blood pressure values significantly decreased at 0 min (mean 112.1 ± 14.82), 15 min (mean 113.6 ± 8.58), 25 min (mean 109.2 ± 8.28) and 30 min (mean 110.8 ± 8.06) compared with the baseline (mean 118.4 ± 8.44).

There were no significant changes in the ketamine group after drug administration, compared with the baseline.

There were no significant differences between the three groups in preoperative, after spinal block, and from 4 to 6 h postoperative.

There was significant decrease in the systolic blood pressure in the three groups after spinal block, DEX group (mean 101.8 ± 16.06), ketamine group (mean 100.9 ± 11.71), and combination group (mean 100.2 ± 11.56) compared with the baseline (mean 118.2 ± 8.06, 118.8 ± 7.50, and 118.4 ± 8.44, respectively) (Fig. 5).

Changes in diastolic blood pressure

There were significant differences among the three groups in the diastolic blood pressure from 0 min until 2 h postoperatively. Compared with the baseline (mean 68.53 ± 10.13), the diastolic blood pressure showed the lowest values in the DEX group at 0 min (mean 63.65 ± 11.25), 3 min (mean 62.06 ± 8.13), 5 min (mean 61.76 ± 8.32), 7 min (mean 60.35 ± 8.55), 10 min (mean 63.53 ± 9.98), and 20 min (mean 58.35 ± 12.80), and the highest value at 2 h (mean 70.65 ± 1.46).

No significant changes were observed in the diastolic blood pressure in the ketamine group after drug administration, with the highest values at 0 min (mean 70.05 ± 10.16) and 15 min (mean 71.53 ± 12.51) compared with the baseline (mean 68.53 ± 11.19).

In the combination group, the diastolic blood pressure showed insignificant changes after drug injection with the lowest value at 30 min (mean 63.87 ± 5.24) compared with the baseline (mean 68.60 ± 9.99).

There were insignificant differences among the three groups preoperative, after spinal block, and from 3 to 6 h after drug administration.

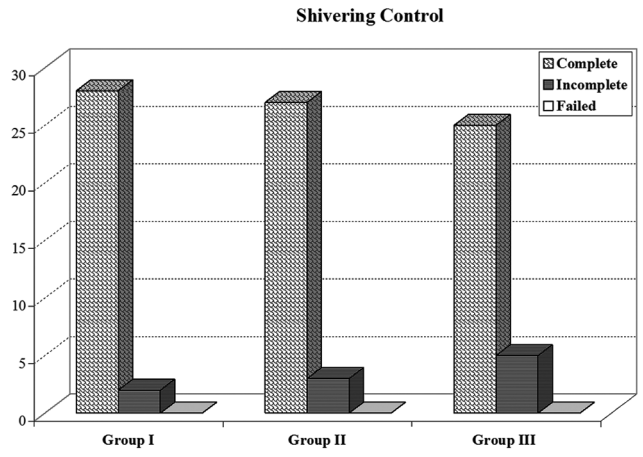
There was significant decrease in diastolic blood pressure in the DEX group, ketamine, and combination groups after spinal block (mean 57.41 ± 9.33, 58.79 ± 8.17, and 57.80 ± 5.02, respectively) compared with the baseline (mean 68.53 ± 10.13, 68.53 ± 11.19, and 68.60 ± 9.99, respectively) (Fig. 6).

Changes in heart rate

Comparison among the groups for the HR value revealed significant differences between groups from 0 until 40 min after study drug injection and from 4 until 6 h postoperatively.

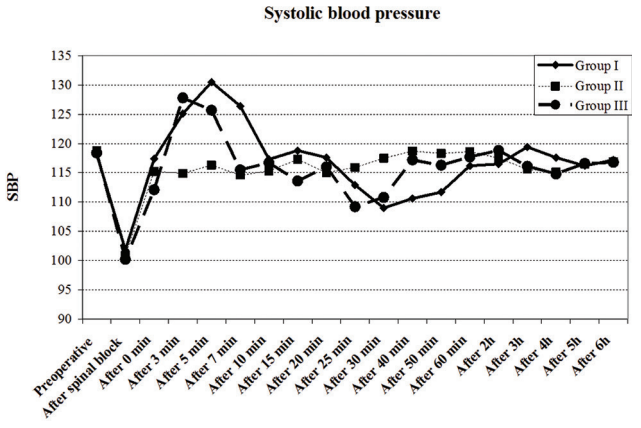
The lowest HR values were observed in the DEX and combination groups, which reached a statistical significance in DEX group at 3 min (mean 77.59 ± 10.49), 5 min (mean 75.94 ± 9.66), 20 min (mean 65.29 ± 9.20), 25 min (mean 78.65 ± 9.20), 30 min (mean 75.76 ± 8.54), and

Figure 4



Shivering control.

Figure 5



Changes in systolic blood pressure.

6 h (mean 79.35 ± 4.16) after drug injection, compared with the baseline (mean 88.0 ± 9.97), where in combination group, the lowest HR values were at 3 min (mean 77.93 ± 10.55), 5 min (mean 79.13 ± 12.51), 20 min (mean 78.53 ± 7.95), 25 min (mean 65.60 ± 8.17), and 30 min (mean 66.53 ± 8.09) compared with the baseline (mean 87.47 ± 8.24).

In ketamine group, there were no significant changes compared with the baseline.

There were insignificant differences between groups preoperatively, after spinal block, and from 50 min until 3 h after study drug injection (Fig. 7).

Changes in core temperature measurements

Comparison among groups for core temperature revealed no significant differences after study drug administration at any time.

No significant changes were revealed in core temperatures in any group.

In DEX group, the highest value was at 120 min (36.71 ± 0.499), where the lowest value at 30 min (36.29 ± 0.437).

In ketamine group, the highest value was at 120 min (36.63 ± 0.93), whereas the lowest value at 15 min (36.23 ± 0.27).

In combination group, the highest value was at 15 min (36.65 ± 0.44), where the lowest value at 150 min (36.16 ± 0.45) (Fig. 8).

Adverse effects

Five (16.66%) patients in the DEX group compared with three (10%) patients in ketamine group and four (13.3%) patients in the combination group were presented with hypotension and were treated with ephedrine 10 mg, i.v., with statistical difference ($P = 0.04$).

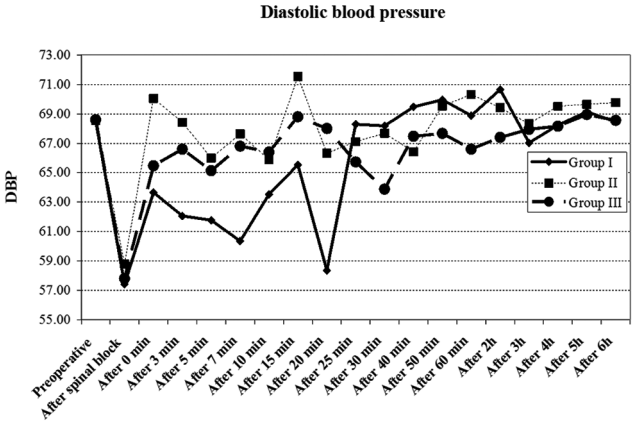
Three patients in the DEX group, compared with two (6.66%) patients in combination group developed bradycardia and were treated with 0.5 mg atropine, i.v., whereas no bradycardia revealed in ketamine group, with no statistical difference.

Two (6.66%) patients in DEX group compared with five (16.66%) patients in ketamine group and three (10%) patients in combination group developed tachycardia with statistical difference ($P = 0.034$).

Nine (30%) patients in the DEX group were compared with 10 (33.3) patients in ketamine group and 11 (37.6) patients in combination group developed sedation (score 3).

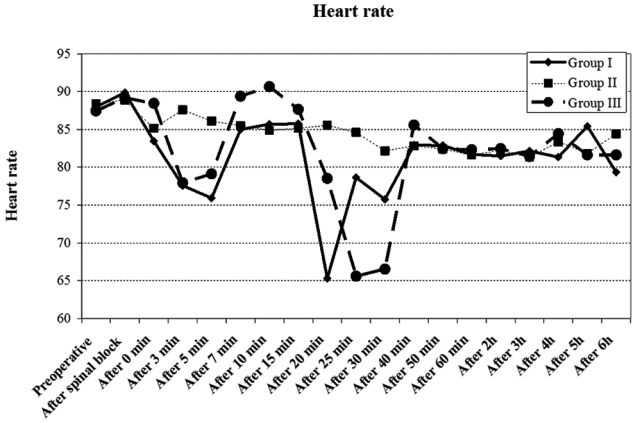
Five (16.66%) patients in ketamine group compared with two (6.66%) patients in combination group developed nausea, with statistical difference ($P = 0.01$).

Figure 6



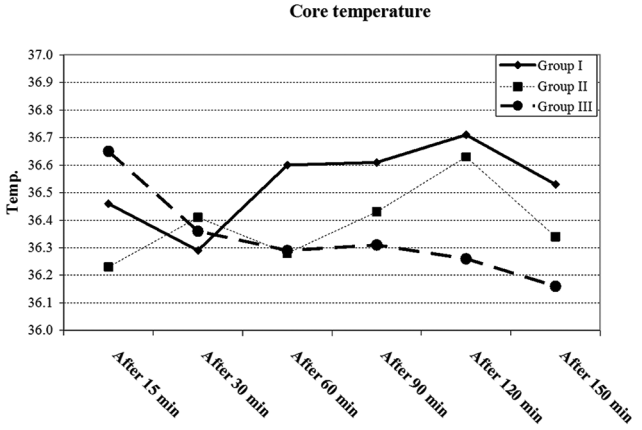
Changes in diastolic blood pressure.

Figure 7



Changes in heart rate.

Figure 8



Changes in core temperature measurements.

No patients developed nausea in dexmedetomidine group

Three (10%) patients in ketamine group compared with two (6.66%) patients in combination group developed headache episodes with statistical difference ($P = 0.04$).

No detection of headache episodes with dexmedetomidine group

Five (16.66%) patients in ketamine group developed hallucinations, whereas no hallucinations detected with DEX or combination groups.

There was no detection of episodes of oxygen desaturation or respiratory depression in any patient during the study.

There were no incidences of other adverse events such as hypertension, vomiting, or arrhythmia in any of the study groups (Table 2).

Discussion

The results of this study revealed that the shivering control in each group was 28% in the DEX group, 27% in the ketamine group, and 25% in combination group.

Shivering-cessation time was significantly lower in DEX group (mean 35.17 ± 6.13) compared with ketamine (mean 39.13 ± 8.11) and combination (mean 42.15 ± 9.16) groups; moreover, shivering recurrence was significantly lower in DEX group (16.67%) than in ketamine (33.33%) and combination group (36.7%).

Recurrence of shivering activity was significantly higher in the combination group [11 (36.7%) patients] and ketamine group [10 (33.33%) patients] compared with the DEX group [five (16.67%) patients] ($P = 0.021$).

From the aforementioned data, we can conclude that the use of DEX achieved higher control of shivering throughout the study within short time and with less recurrence, compared with the ketamine and the combination.

In a study by Blaine Easley *et al.* [4], all children who had postanesthesia shivering were treated with a single i.v. bolus dose of DEX 0.5 μg/kg over 3–5 min. All children had cessation of shivering behavior within 5 min following the completion of DEX administration, and there was no recurrence of shivering.

In a study by Usta *et al.* [5], it was found that DEX exerts its dual effects while avoiding vasoconstriction and increasing the level of the shivering threshold. Their study included sixty patients with ASA status I and II aged 18–50 years scheduled for elective minor surgical operations under spinal anesthesia with hyperbaric bupivacaine. Patients were allocated to one of two groups: group C ($n = 30$) received normal saline and group D ($n = 30$) received DEX i.v. The intensity of shivering was lower in group D than in group C ($P = 0.001$). Time from baseline to onset of shivering was 10 (5–15) min in group D and 15 (5–45) min in group C ($P = 0.207$).

Shakaya and Chaturvedi [6] evaluated the efficacy of low-dose ketamine 0.25 mg/kg and ondansetron 4 mg for prevention of shivering during spinal anesthesia in 120 patients undergoing lower abdominal surgery. Their results show that ketamine was more effective in controlling shivering, as shivering was observed in 10% in ondansetron group compared with 2.5% in ketamine group.

The study by Shreyavathi *et al.* [7] was conducted in 100 ASA grade I and II patients. They were allocated into four groups of 25 each and were given saline in control (group S), ketamine 0.5 mg/kg (group K), clonidine 75 μg (group C), and 1 mcg/kg (group D) i.v. before subarachnoid block. There was no incidence of statistically significant shivering in ketamine, clonidine, and DEX groups.

The study by Mittal *et al.* [8] found that time taken for cessation of shivering was significantly less with DEX when compared with tramadol. Their study was conducted in 50 patients of ASA status I and II aged between 18 and 65 years, scheduled for various surgical

Table 2 Adverse effects

Adverse effects	Group I dexmedetomidine (n=30) [n (%)]	Group II ketamine (n=30) [n (%)]	Group III mix. (n=30) [n (%)]	P
Hypotension	5 (16.66)	3 (10)	4 (13.3)	0.04*
Hypertension	-	-	-	-
Bradycardia	3 (10)	-	2 (6.66)	NS
Tachycardia	2 (6.66)	5 (16.66)	3 (10)	0.034*
Sedation	9 (30)	10 (33.3)	11 (36.7)	0.05*
Nausea	-	5 (16.66)	2 (6.66)	0.01**
Vomiting	-	-	-	-
Arrhythmia	-	-	-	-
Headache	-	3 (10)	2 (6.66)	0.04*
Hallucination	-	5 (16.66)	-	-

*Statistically significant; **Highly statistically significant

procedures under spinal anesthesia. The patients were randomized in the two groups of 25 patients, each to receive either DEX 0.5 μg/kg or tramadol 0.5 mg/kg as a slow i.v. bolus, and there was not much difference in the sedation profile.

Few studies that have explored its anti-shivering potential have inferred that DEX is an effective drug without any major adverse effect and provides good hemodynamic stability.

In this study, the hemodynamic instability recorded with DEX administration whether in DEX group or combination group is not uncommon and treated with fluid infusion, vasopressors, and atropine.

There was no hemodynamic instability in systolic or diastolic blood pressures recorded in ketamine group after drug administration, but insignificant tachycardia was recorded in five patients and did not needed any treatment.

The study by Sagir *et al.* [9] found that ketamine administration was not associated with significant hypertension and tachycardia, similar to our results.

In this study, there were no statistically significant differences in core temperature among all groups at any time of the study.

In a study by Usta *et al.* [5], it was found that hypothermia was observed in 21 (70%) patients in DEX group and in 20 (66.7%) patients in control group.

Incidence of adverse effects was more in ketamine and combination groups, such as nausea was seen in 16.66% in ketamine group and in 6.66% in combination group compared with none in DEX group.

Hallucinations were more in ketamine group at 16.66% compared with none in the other groups.

Headache was more in ketamine group at 10% and combination group at 6.66% compared with none in the DEX group.

Shukla *et al.* [10] reported the incidence of nausea was quite high at 77.5% with DEX, whereas the study by Wason *et al.* [11] reported the incidence of nausea at only 4% with DEX, which is in contrast with our results.

Sagir *et al.* [9] observed that patients may develop hallucinations and postoperative nausea or vomiting with ketamine.

The study by Mittal *et al.* [8] found that nausea and vomiting were not observed in DEX group and observed only in tramadol group (28 and 20%, respectively).

Conclusion

We concluded that i.v. DEX 0.4 mcg/kg, i.v., ketamine 0.3 mg/kg, or combination between DEX 0.25 mcg/kg and ketamine 0.25 mg/kg significantly controlled the shivering that occurred during spinal anesthesia. However, DEX is superior to ketamine and the combination in prevention of shivering.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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