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Research Article

Efficacy of prophylactic use of hydrocortisone and low dose ketamine for prevention of shivering during spinal anesthesia

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KEYWORDS

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Abstract *Background:* Spinal anesthesia is commonly associated with shivering. The aim of this study was to compare the efficacy of i.v. hydrocortisone with i.v. low dose ketamine or placebo for prevention of shivering during spinal anesthesia.
Method: In this prospective, randomized, double-blind study, 90 female patients ASA I–II age 30–60 years old, undergoing posterior vaginal repair surgeries under spinal anesthesia with 3 ml heavy bupivacaine 0.5% (15 mg), patients were randomly allocated into one of three groups, (Group S, $n = 30$) (control) received saline, (Group K, $n = 30$) received ketamine 0.25 mg kg^{-1} or (Group H, $n = 30$) received hydrocortisone 2 mg kg^{-1}, the drugs were given i.v. just after spinal anesthesia with recording of vital signs, and core temperature every 15 min intraoperative and every 10 min in recovery room. The incidence and intensity of shivering, number of patients received meperidine, sensory level, motor block grade, and side effects (hypotension, hypertension, tachycardia, nausea and vomiting, sedation and hallucinations) were also recorded.
Results: Incidence of shivering were significantly reduced in k and H groups being 20% and 23.3% respectively compared to S group ($p < 0.05$). Patients received meperidine to control shivering were significantly low in Groups K and H compared to group S ($p < 0.05$), with no difference between Groups K and H.

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Conclusions: The prophylactic administration of low dose ketamine (0.25 mg kg^{-1}) and hydrocortisone (2 mg kg^{-1}) were comparable in reducing the incidence of shivering and both had significant antishivering effect compared to placebo, in female patients under spinal anesthesia for posterior vaginal repair surgeries.

1. Introduction

Shivering is a common problem during spinal anesthesia because of hypothermia that lowers the threshold for shivering which induce tachycardia, hypertension, and increase oxygen consumption by 400–500% [1]. Also, it interferes with ECG and blood pressure monitoring [2]. Hypothermia under spinal anesthesia is due to core to peripheral redistribution of heat, loss of vasoconstriction below the level of the block with increase of heat loss from body surfaces, and altered thermoregulation with decrease in shivering thresholds [3].

A high level of spinal block is known to decrease the core temperature, the core temperature decreases by 0.15 °C, for each dermatome increase in block level [1].

Many drugs have been used for prevention of shivering including opioids meperidine; the non-opioid analgesic tramadol; the 5-HT3 antagonists ondansetron; the cholinomimetic agent physostigmine; alpha 2 adrenergic agonist clonidine [3].

Ketamine, a competitive N-methyl D-aspartate (NMDA) receptor antagonist, which has been shown to inhibit postoperative shivering in many reports [4–7].

Hydrocortisone, a glucocorticoid member, which has been found to be effective in the prevention of postoperative shivering in the study of Pawar et al. [8], may be through affecting the protein, fat, carbohydrate, and purine metabolism, and a direct calorigenic effect.

To our knowledge, there is no study comparing hydrocortisone with ketamine as a prophylactic antishivering agent. This prospective, randomized, double-blind, placebo controlled study was designed to compare i.v. hydrocortisone and i.v. low dose ketamine for the prevention of shivering in female patients who underwent posterior vaginal repair surgeries under spinal anesthesia.

2. Method

After approval of the local ethical committee, a written informed consent obtained from 90 female patients ASA I and II aged 30–60 years old, planned for posterior vaginal repair surgeries under spinal anesthesia in Beni Sueif university hospital from September 2011 to February 2012.

Patients were excluded from the study if they had history of convulsions, hypertension, coronary artery disease, thyroid dysfunction, diabetes, peptic ulcer, or on prolonged steroid therapy, those with known allergy to amide local anesthetic or to the study drugs, expected blood transfusion during surgery or any contraindication to regional anesthesia (e.g. local infection, coagulation abnormality, tight valvular heart lesion or patient refusal) or BMI > 30 or an initial body temperature > 38 °C or < 36 °C.

The study protocol was explained to each patient during the preoperative visit. No premedication was given to the patients. On arrival to the operating theatre, the patients were put in the induction room where 18 G intravenous cannula was inserted and IV warmed crystalloid fluids (37 °C) using level 1 hot fluid warmer (Rockland, MA, USA) was given at a rate of 10 ml kg^{-1} over 30 min before spinal anesthesia then the rate was reduced to 6 ml kg^{-1} h^{-1}.

The patients were randomly divided using closed envelope technique for randomization to one of three groups: control group (Group S, $n = 30$) received saline, (Group K, $n = 30$) received ketamine 0.25 mg kg^{-1} or (Group H, $n = 30$) received hydrocortisone 2 mg kg^{-1}.

The studied drugs were diluted in 5 ml coded syringes and the normal saline and given as an i.v. bolus just after intrathecal injection, by an anesthesiologist who was unaware to the drugs given.

With adjustment of the temperature in operating room at 22 °C, the patients were shifted to the operating room where the monitor was attached to the patients to take preoperative readings of heart rate, non-invasive arterial blood pressure, Spo_2, and tympanic membrane temperature using FirstTemp Genius Model 3000 (Sherwood Medical Company, St. Louis, UK).

Spinal anesthesia was performed under strict aseptic technique in the sitting position, at L3–L4 or L4–L5 space, with 3 ml heavy bupivacaine 0.5% (15 mg), and the patients were put in the supine position, supplemented with oxygen 4 L/min by face mask, covered with surgical drapes but not warmed actively, and monitored with ECG (lead II and V with ST segment analysis), pulse oximetry, and non-invasive arterial blood pressure measured every 5 min, and core temperature were monitored.

At the end of surgery, the patients were shifted to the recovery room, where patients were monitored, covered with one cotton blanket receiving supplemental oxygen (4 L/min) by facemask with adjustment of the recovery room temperature at 22 °C.

The following parameters were evaluated in all patients by an anesthesiologist unaware of the study drugs:

1. Patient characteristics and operation time.
2. Core temperature (tympanic membrane temperature) before and immediately after the completion of intrathecal injection and every 15 min after spinal anesthesia and every 10 min in the recovery room.
3. Shivering intensity was graded by using a five-point scale that was used in the study of *Honarmand and Safavi* [3]: (Grade 0: none; Grade 1: one or more areas of piloerection but without visible muscular activity; Grade 2: visible muscular activity confined to one muscle group; Grade 3: same as Grade 2 but in more than one muscle group; and Grade 4: gross muscular activity involving the entire body). If shivering grades $\geqslant 3$ was

observed after spinal anesthesia and administration of one of the studied drugs, the patients were treated with i.v. meperidine 25 mg or using a heating blankets (Bair Hugger® warming unit, Arizant Healthcare Inc., USA) in sedated patients.
4. The incidence of shivering.
5. Number of patients requiring meperidine.
6. Sensory level was assessed by loss of cold perception to ice 5 min after the completion of spinal anesthesia.
7. Motor block was evaluated by Bromage motor scale [9]: (1, unable to move feet; 2, able to move feet only; 3, just able to move knees; and 4, full flexion of knees and feet) 5 min after the completion of spinal anesthesia.
8. Heart rate, mean arterial blood pressure, and peripheral oxygen saturation recorded (intraoperatively before spinal anesthesia and every 15 min after spinal anesthesia, and every 10 min in the recovery room).
9. Side effects:

– nausea and vomiting (treated with metoclopramide 10 mg i.v.),
– hypotension (decrease in MAP > 20% from preoperative reading and was treated by i.v. fluids and ephedrine 6 mg i.v.),
– hypertension (increase in MAP > 20% from preoperative reading),
– tachycardia (increase in HR > 20% from preoperative reading,
– hallucination (false sensory experience),
– sedation (graded on a five-point scale: (1) fully awake and oriented; (2) drowsy; (3) eyes closed, arousable to command; (4) eyes closed, arousable to physical stimulation; and (5) eyes closed, unrousable to physical stimulation). [10]

3. Statistical analysis

We calculated the sample size of 30 patients in each group using the programme of Biostatics version 3.01 based on the data from previous studies that found the shivering incidence was 40–65% and we took the incidence of 45% in the control group and 40% difference between control and treated groups with the α-error level was fixed at 0.05 and the power was set at 90%. Data values are presented as means (SD), median (range) or number (percentage). Parametric data were analyzed by using one way ANOVA and Student's paired *t*-test where appropriate. Nonparametric data were analyzed by using the Kruskal–Wallis test. A value of $P < 0.05$ was considered significant. All statistical analysis was performed using Microsoft Excel.

Table 1 Patient characteristics and operative data.

Variables	Group S ($n = 30$)	Group K ($n = 30$)	Group H ($n = 30$)
Age (years)	46(14)	46(14)	44(14)
Weight (kg)	79(9)	80(8)	81(8)
Height (cm)	168(6)	169(6)	168(6)
ASA physical status (I/II)	12/18	13/17	11/19
Operation time (min)	58(3)	58(4)	59(3)

Group S: Saline group, Group K: ketamine group, Group H: hydrocortisone group.
Data presented as mean (SD) or number.
No significant differences among the studied groups.

4. Results

There were no significant differences among the three groups regarding age, weight, height, ASA grade, and operation time (Table 1).

Incidence of shivering was significantly reduced in K and H groups being 20% and 23.3% respectively, compared to S group being 60% ($p < 0.05$). Grade 0 shivering was significantly high in Groups K and H compared to group S ($p < 0.05$), with no difference between Groups K and H. Grade 3 and 4 shivering was significantly low in Groups K and H compared to group S ($p < 0.05$), with no difference between Groups K and H. Patients received meperidine were significantly low in Groups K and H compared to Group S ($p < 0.05$), with no difference between Groups K and H. (Table 2).

Core temperature recorded every 15 min intraoperative in all patients in the three groups decreased in comparison to preoperative reading, these decrease were statistically insignificant. The decrease in temperature was more in H and S groups than in K group, but the decrease was statistically insignificant at every measurement between the three groups (Table 3).

There were no significant differences in hemodynamic changes (HR and MAp) and peripheral O_2 saturation among the three groups at different times of recording (Table 4).

There were no significant differences in sensory level and motor block grade among the three groups. (Table 5).

Sedation was seen in all patients in K group (100%), 18 cases of them were of Grade 2 and 12 cases were of Grade 3, without sedation was recorded in H and S groups. There were no significant differences among the three groups regarding hallucination, hypotension, hypertension and nausea and vomiting. (Table 6).

Table 2 Incidence and severity of shivering and number of patients received meperidine.

Variables	Group S ($n = 30$)	Group K ($n = 30$)	Group H ($n = 30$)
Patients developed shivering (*n*)	18 (60)	6 (20)*	7 (23.3)*
Grades of shivering			
Grade 0	12 (40)	24 (80)*	23 (76.6)*
Grade 1	3(10)	3(10)	3(10)
Grade 2	3(10)	2 (6.6)	2 (6.6)
Grade 3	7 (23.3)	1 (3.3)*	1 (3.3)*
Grade 4	5(16.7)	0 (0)*	1 (3.3)*
Number of patients received meperidine(n)	*12 (40)*	*0 (0)**	2 (6.6)*

Group S: Saline group, Group K: ketamine group, Group H: hydrocortisone group.
Data presented as number (percentage).
* Significant difference ($p < 0.05$) Compared to Group S.

Table 3 Core temperature.

Temperature	Group S (n = 30)	Group K (n = 30)	Group H (n = 30)
Preoperative	36.7(0.1)	36.7(0.1)	36.8(0.13)
Intraoperative			
T0	36.6(0.1)	36.7(0.1)	36.6(0.1)
T15	36.1(0.1)	36.4(0.1)	36 (0.1)
T30	35.8 (0.1)	36.2(0.1)	35.9(0.2)
T45	35.6(0.1)	36.1(0.1)	35.6(0.1)
T60	35.4(0.1)	35.9(0.1)	35.4(0.1)
In recovery room			
T10	35.5(0.1)	35.7(0.1)	35.6(0.1)
T20	35.6(0.1)	35.6(0.1)	35.6(0.1)
T30	35.5(0.1)	35.6(0.1)	35.6(0.1)

Group S: Saline group, Group K: ketamine group, Group H: hydrocortisone group.
Data presented as mean (SD), T0: immediately after spinal anesthesia, T15: 15 min after spinal anesthesia, T30: 30 min after spinal anesthesia, T45: 45 min after spinal anesthesia, T60: 60 min after spinal anesthesia, T10: 10 min in recovery, T20: 20 min in recovery, T30: 30 min in recovery.
No significant differences among the studied groups.
No significant differences compared to preoperative reading.

Table 5 Sensory level and motor block grade.

Variables	Group S (n = 30)	Group K (n = 30)	Group H (n = 30)
Sensory level(dermatome)	T8(T6 – T10)	T8(T6 – T8)	T8(T6 – T10)
Motor block grade	2(1–2)	1(1–2)	2(1–2)

Group S: Saline group, Group K: ketamine group, Group H: hydrocortisone group.
Data presented as median (range).
No significant differences among the studied groups.

5. Discussion

In this study, our results indicate that i.v. hydrocortisone 2 mg/kg was effective as iv ketamine 0.25 mg/kg in reducing the incidence and intensity of shivering during spinal anesthesia compared to control group with advantage of hydrocortisone over ketamine as being not associated with sedation.

In this study, the incidence of shivering in hydrocortisone group was 23.3% compared to 60% in control group. our results are in agreement with the studies done by Pawar et al. [8] who reported that hydrocortisone (1–2 mg kg^{-1} iv) was effective in prevention of postoperative shivering after knee arthroscopy under general anesthesia where the incidence of shivering was 20% and 32% with hydrocortisone 2 mg·kg^{-1} and 1 mg·kg^{-1} respectively compared to 60% in control group and Qioa et al. [11] showed that hydrocortisone 2 mg kg^{-1} iv was effective in treating post-spinal anesthesia shivering in caesarean section. The mechanism of hydrocortisone prevention of shivering is unclear. It could be that corticosteroids have an anabolic effect or through alterations in thyroid hormone metabolism or nitric oxide synthase activity [8].

In this study the incidence of shivering in ketamine group was 20% compared to 60% in control group. This is in consistence with many studies that reported the effectiveness of ketamine in prevention of postoperative shivering, Norouzi et al. [4] reported that ketamine 0.25 mg kg^{-1} and 0.5 mg kg^{-1} was a good prophylactic drug for prevention of postanesthetic shivering, Shakya et al. [5] concluded that low dose ketamine 0.25 mg·kg^{-1} compared with ondansetrone 4 mg was effective in prevention of shivering in lower abdominal surgery under spinal anesthesia, Dal et al. [6] found that ketamine 0.5 mg kg^{-1} iv was effective like pethedine 20 mg in prevention of the postoperative shivering after general anesthesia and Kose et al. [7] found that iv ketamine 0.5 and 0.75 mg kg^{-1} iv ketamine was effective as meperidine 25 mg for the treatment of postoperative shivering. Ketamine prevents shivering by non-shivering thermogenesis at the level of the hypothalamus or the beta adrenergic action of nor epinephrine [3]. Because of all patients in ketamine group showed a degree of

Table 4 Hemodynamic changes and peripheral O_2 saturation.

Time	Group S (n = 30)			Group K (n = 30)			Group H (n = 30)		
	HR	MAP	Spo_2	HR	MAP	Spo_2	HR	MAP	Spo_2
Intraoperative									
T0	79(6)	95(3)	97(1)	79(5)	94(2)	96(2)	78(5)	95(3)	97(1)
T15	78(6)	91(2)	98(1)	77(5)	89(3)	98(1)	78(6)	88(3)	98(1)
T30	76(4)	89(2)	99(1)	75(4)	85(3)	99(1)	75(5)	87(2)	99(1)
T45	75(3)	91(3)	98(1)	73(4)	84(3)	99(1)	73(3)	88(2)	99(1)
T60	74(6)	88(2)	99(1)	72(4)	89(2)	98(1)	75(3)	89(2)	98(1)
In recovery room									
T10	69(6)	88(2)	98(1)	73(2)	88(2)	98(1)	70(3)	85(3)	98(1)
T20	71(3)	89(2)	98(1)	73(2)	89(2)	98(1)	69(5)	84(3)	99(1)
T30	72(3)	91(3)	99(1)	68(5)	90(2)	99(1)	68(6)	89(2)	99(1)

Group S: Saline group, Group K: ketamine group, Group H: hydrocortisone group.
Data presented as mean (SD), HR: heart rate, MAP: mean arterial pressure, Spo2: peripheral oxygen saturation,T0: immediately after spinal anesthesia, T15: 15 min after spinal anesthesia, T30: 30 min after spinal anesthesia, T45: 45 min after spinal anesthesia, T60: 60 min after spinal anesthesia, T10: 10 min in recovery, T20: 20 min in recovery, T30: 30 min in recovery.
No significant differences among the studied groups.

Table 6 Side effects.

Variables	Group S (n = 30)	Group K (n = 30)	Group H (n = 30)
Nausea and vomiting	0(0)	0(0)	0(0)
Hallucination	0(0)	0(0)	0(0)
Hypotension	0(0)	0(0)	0(0)
Hypertension	0(0)	0(0)	0(0)
Sedation			
Grade 1	0(0)	0(0)	0(0)
Grade 2	0(0)	18(60)*	0(0)
Grade 3	0(0)	12(40)*	0(0)
Grade 4	0(0)	0(0)	0(0)
Grade 5	0(0)	0(0)	0(0)

Group S: Saline group, Group K: ketamine group, Group H: hydrocortisone group.
Data presented as number (percentage).
* Significant difference ($p < 0.05$) compared to other two groups.

sedation, the patients developed shivering of Grade 3 or more were treated with heating blankets, not with i.v. meperidine.

In this study the core temperature measured through tympanic membrane decreased during intraoperative period in the three groups compared to preoperative reading. The decrease in temperature was clinically significant but statistically insignificant. The hypothermia during spinal anesthesia can be explained by heat redistribution from core to periphery, vasodilatation with heat loss and inhibition of thermoregulation. The decrease in temperature was less significant in ketamine group than hydrocortisone and saline groups; this may be due to vasoconstrictive effect of ketamine. This is in consistence with the study of Shakya et al. [5] who found decrease of temperature in ketamine (0.25 mg kg^{-1}) group was less than in ondansetrone and saline groups during spinal anesthesia. In the study done by Sagir et al. [12], the decrease of core temperature was more in control group than ketamine (0.5 mg kg^{-1}) group. However, Pawar et al. [8], found the decrease of core temperature during anesthesia was similar between hydrocortisone (1–2 mg kg^{-1}) group and saline group during knee arthroscopy.

The hemodynamic parameters (heart rate and mean arterial pressure) in our study were comparable among the three groups. This is in agreement with the studies of Shakya et al. [5], Dal et al. [6], and Sagir et al. [12] who found no hemodynamic changes associated with ketamine, also, no hemodynamic changes associated with hydrocortisone (single dose) in the studies done by Pawar et al. [8], Keh et al. [13], and Jules-Elysee et al. [14].

In this study all patients in ketamine group developed sedation, 18 cases of them were of Grade 2 and 12 cases were of Grade 3 without hallucination. This is in consistent with the result of Shakya et al. [5], who found sedation in 95% of patients without hallucination with ketamine 0.25 mg kg^{-1}. Hypotension was not recorded in this study because of fluid preloading before spinal anesthesia. Also, nausea and vomiting were not observed in any of patients in this study, although it is a known side effect of ketamine, may be because of low dose ketamine 0.25 mg kg^{-1} used in this study, this is in agreement with Shakya et al. [5].

It is found that ketamine 0.5 mg kg^{-1} iv was effective like pethedine 20 mg in prevention of the postoperative shivering after general anesthesia [6], however we did not find a study comparing hydrocortisone with pethedine.

In conclusion, the prophylactic administration of low dose ketamine (0.25 mg kg^{-1}) and hydrocortisone (2 mg kg^{-1}) were comparable in reducing the incidence of shivering and both had significant antishivering effect compared to placebo, in female patients under spinal anesthesia for posterior vaginal repair surgeries.

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