Intravenous Ketamine for the Prevention of Post Anesthetic Shivering in Spinal Anesthesia: A Randomized Double-Blind Placebo-Controlled Trial

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Abstract- Spinal anesthesia (SA) may impair thermoregulatory control, which may result in shivering, which is a potentially harassing complication. The aim of the current study was to evaluate the prophylactic effects of intravenous ketamine on the prevention of shivering in patients who underwent elective cesarean section (CSs) under SA. In this double-blind, randomized placebo controlled trial, a total of 90 parturients under SA using hyperbaric bupivacaine 12.5 mg were allocated in two groups to receive ketamine 0.3 mg/kg or 0.9% saline following delivery. After induction of SA, patients were observed for the incidence and intensity of shivering using a four-point scale. Shivering was observed in 24 patients (53.3%) in the saline group and 15 patients (33.3%) in the ketamine group. Median (quartiles 1 and 3) of the intensity of shivering was 1 (0-2) and 0 (0-2) in saline and ketamine groups, respectively. Time from spinal anesthesia to the beginning of shivering was 33.1±11.7 min in saline versus 41.6±20.7 min in the ketamine group. The incidence of nausea, vomiting, hypotension, and bradycardia was not different between the groups. A significantly higher incidence of nystagmus and sedation was observed in the ketamine group when compared with the saline group administration of low dose i.v. Ketamine (0.3 mg/kg) was effective in lowering shivering intensity during CSS under spinal anesthesia, though side effects such as nystagmus and sedation may restrict its effectiveness.

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Introduction

Spinal anesthesia (SA) may impair thermoregulatory control and lead to shivering, which can be an unpleasant part of the birth experience for parturients (1). Postoperative shivering occurs in a total of 36 to 85% of patients after SA (2) and 36 to 71% of cesarean section (CSs) done under SA (3). Shivering is a potentially unpleasant and harmful complication, which may cause increased metabolic activity, oxygen consumption, carbon dioxide production, ventilation, cardiac output, circulating catecholamines, and postoperative pain. Moreover, it also interferes with the monitoring of blood pressure, heart rate, electrocardiogram, and pulse oximetry (3-6). Therefore, it is important to prevent shivering during SA. There are many pharmacological methods to treat shivering during SA block, while studies that emphasize its prevention are rare.

Ketamine, a competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has a role in thermoregulation and has been shown to have antishivering properties in doses of 0.5 to 0.75 mg/kg during SA (6,7). But following the use of these doses, side effects, such as drowsiness, hallucination, delirium, and postoperative cognitive dysfunction may appear (8). Thus, it may be reasonable to examine the lower doses of ketamine for this purpose.

Kose *et al*., (9) examined the prophylactic effect of two different doses of ketamine in the prevention of shivering in CSs during SA with 15 mg bupivacaine. They found that the incidence of shivering decreased from 37% to 6.6% and 3.3% by 0.25 and 0.5 mg/kg prophylactic ketamine, respectively. They warmed the patient actively by forced-warm air during operation.

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This may influence the results, leading to doubts about the exact effect of low dose ketamine alone on the prevention of shivering during SA for CSs.

It was hypothesized that administration of low dose i.v. Ketamine (0.3 mg/kg) following SA block will reduce the incidence and intensity of shivering and decrease the need for rescue drugs to control shivering. So, this prospective, double-blind, randomized placebo controlled study was performed to examine this hypothesis that intravenous ketamine might decrease the incidence of shivering in patients who underwent elective CSs under SA. The primary endpoint of our study was to evaluate the effect of IV ketamine on the incidence of intraoperative and postoperative Shivering. Meanwhile, the severity of shivering, level of sedation, and side effects from the administration of study medication were the secondary endpoint. While most previous studies focused on treating shivering, emphasis on prevention is the novelty of current research.

Materials and Methods

Design

This parallel randomized, double-blind placebo controlled trial was performed after approval by the Institutional Clinical Research Ethics Committee and registration of the study at the Registry of Clinical Trials. The protocol is available in the research deputy at our University.

Participants who were scheduled for elective cesarean section (CSs) under SA how_aged 18-45 years were included in the study after receiving written informed consent. Patients with any contraindications for SA, history of spinal surgery, preeclampsia, hypo- or hyperthyroidism, pulmonary or systemic hypertension, cardiopulmonary disease, neurological disorders, known history of addiction, need for analgesic or sedative drugs due to inadequacy of blocks during the procedure, history of sensitivity to study drugs, American Society of Anesthesiologists (ASA) physical status≥ III, and those who needed a blood transfusion during surgery were excluded.

Randomization numbers were generated by Random Allocation software (version 1) using a simple randomization method, and the numbers were put in some envelopes. From 113 cases, 95 participants met inclusion criteria, and after obtaining written informed consent, they were randomized by an anesthetic nurse who is not involved in the outcome evaluation. During the study, 5 participants were excluded due to inadequate level of the block and changing method of anesthesia (Figure 1).

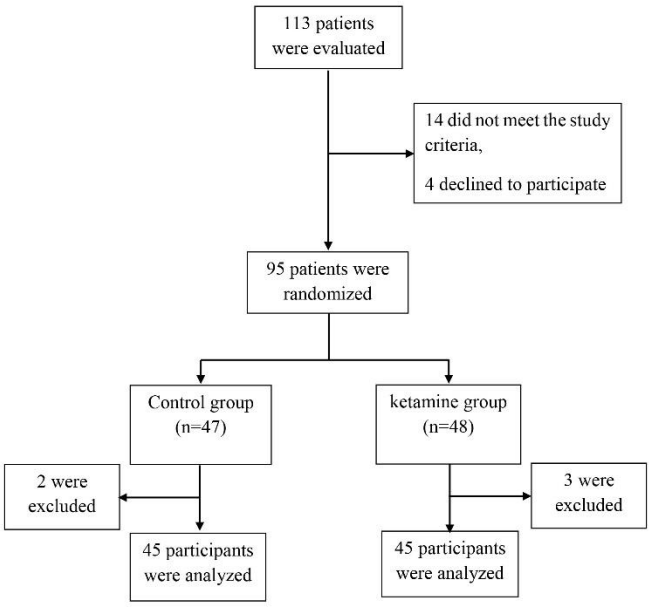

Figure 1. Profile of the participants of the study

Pre-anesthetic interventions

Demographic data were recorded in the holding room. On arrival in the operating room, blood pressure, electrocardiogram (ECG), and SpO_2 were monitored, and basic values were recorded and 10 ml/kg of lactated Ringer's solution that was preheated to 37° C was infused over 15 min for all patients. Monitoring and recording of hemodynamic data were continued at 5 min intervals

during surgery tell discharge from the post-anesthesia care unit (PACU). Axillary temperature was recorded using an axillary thermometer before SA block at 10 min intervals during the perioperative period.

Study interventions

After randomization, SA was accomplished in a sitting position at L3-4 or L4-5 interspaces with a 25G spinal Quincke tip needle. Hyperbaric bupivacaine 2.5 ml of 0.5% solution (12.5 mg) was injected intrathecally. Cases with inadequate sensory block, which led to the change of the anesthesia method, were excluded from the study and replaced with another case.

After SA block administration, patients were covered with one layer of surgical drapes over the whole body besides the head and neck; after being sure about the adequacy of the block by skin pinching, an incision was made, and the baby was delivered. After delivery, one of the study drugs, which consist of ketamine 0.3 mg/kg in the study group (Group K) and 0.9% saline in the control group (Group S), was given as i.v. Bolus by an anesthetist who was not involved in the management of patients. Study drugs were prepared and diluted to a volume of 5 ml and were presented as coded syringes. All patients received oxygen (5 L/min) via a facemask during the operation and were under close observation by a blinded anesthesiologist continuously for the incidence and intensity of shivering. Following the study drug administration, any side-effects such as nausea, vomiting, hypotension, bradycardia, tachycardia, hallucinations, sedation, and nystagmus were recorded in 15 min intervals. Time from SA to the beginning of shivering, maximal heights of sensory block, and duration of surgery (duration from skin incision to dressing), were recorded. At the end of the surgery, patients were transferred to PACU. Patients were covered with one cotton blanket in PACU, and no active warming was used. Patients were observed in the PACU by anesthetic nurses who received training regarding data collection for this study. These nurses were blinded as to the patients' groups. Assessment of side effects and other study outcome variables were continued until an adequate Aldrete score for discharge from the PACU was achieved. Patients did not receive any other sedatives or analgesics while they were in the operating room.

Blinding

Patients were unaware of their groups. Also, the outcomes of the study were evaluated by an investigator who wasn't otherwise involved in the preparation and injection of study drugs. Thus, the study was double-blinded.

Tools and measurements

The ambient temperature of the operating room and post-anesthesia care unit (PACU) was measured using a digital wall thermometer and maintained at 24 to 28° C during surgery. Shivering incidence was the main outcome, and drug adverse or complications were considered as the secondary outcomes. The shivering score was graded on a scale of 0 to 3 as 0=no shivering; 1=shivering in face and neck; 2=muscular activity in more than one muscle group, but not generalized; and 3=shivering involving the whole body. If in the operation room and/or PACU, a score of 2 or 3 of shivering was noted, then the prophylaxis was considered as ineffective, and 30 mg of intravenous pethidine was administered. Maximal heights of sensory blocks were measured using the cold sensation method. Time from SA to the beginning of shivering and duration of surgery (time from skin incision to dressing) were also recorded. Hypotension and bradycardia were defined as a decrease in mean arterial pressure (MAP) of more than 20% from baseline and heart rate (HR) less than 50 beats/min, respectively. Hallucination was defined as an experience in which patients reported they saw, heard, felt, or smelled something that does not exist. The depth of sedation was quantified with a five-point scale used previously by Tasui *et al*., (10): 0=fully awake; 1=drowsy; 2=closed eyes, opens to call; 3=closed eyes, opens to physical stimuli; 4 = closed eyes, nonresponsive to painful stimuli. Patients with nausea or vomiting, hypotension, bradycardia, and hallucinations were treated with metoclopramide, crystalloid infusion, and, if necessary, ephedrine, atropine, and midazolam, respectively, in titrated doses when required.

Data analysis

It seems that 52% of the patient's suffering shivering following neuraxial anesthesia (11). To be able to detect a 25% absolute difference in the incidence of shivering between the groups (control and intervention incidences of 52% and 27%, respectively) with 80% power at the 5% significance level, a sample size of 38 cases per group was required that we studied 45 participants in each group.

All statistics were analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). The age, ambient temperatures, duration of surgery, sensory block levels, and the time from SA to the beginning of shivering were compared using the Student's t-test, or a Mann-Whitney U-test were appropriate for finding significant differences and

considering them in multivariate analysis. Normality of distribution was assessed by Kolmogorov–Smirnov test, and ordinal variables were considered as a non-normal distribution. The incidences (and relative risk) of side effects and scores of shivering and sedation were analyzed using chi-square and Fisher's exact tests. The results are shown as mean (±standard deviation), median (quartile 25 and 75%), and exact numbers or proportions are expressed as a percentage. A $P<0.05$ was considered statistically significant. Power analysis was done at the end for the primary outcome to assess the end power of the study.

Results

In the current study, 95 out of 113 participants met inclusion criteria, which were randomized into two equal groups of 48. Due to the inadequate level of the subarachnoid block and changing method of anesthesia to general anesthesia, 5 participants (2 of control and 3 of the study group) were excluded from the study (Figure 1).

The mean age of participants was 30.3 (±4.6) years. There were no clinically significant differences between the two study groups with respect to age, height, weight, BMI, duration of surgery, post-anesthesia axillary temperature, duration of anesthesia, and the ambient temperature of the operation room and PACU (Table 1).

None of the patients in either group experienced shivering before administration of study drugs, However, shivering as a primary outcome was observed in 24 patients (53.3%) in the normal saline group and 15 patients (33.3%) in the ketamine group (RR=0.62; 95%CI_{RR}:0.38-1.02) after baby delivery and administration of study drugs. According to the primary outcome, the final power of the study was 48.3%.

Median (quartiles 1 and 3) of the intensity of shivering was 1 (0-2) and 0 (0-2) in the normal saline and ketamine groups, respectively. The onset time of shivering in the ketamine and normal saline group was 41.6 (±20.7) and 33.1 (±11.7) minutes, respectively (Table 2). Pethidine was given as a rescue drug in 19 (42.2%) patients in the normal saline group and 13 (28.9%) patients in the ketamine group (P=0.03), which showed a score of 2 or more of shivering; this was effective in all cases.

Table1. Data Related to Patients' and block

Variables	Normal Saline (n=45)	Ketamine (n=45)	Mean differences (95% CI)
Age (year)	29.8 (±4.5)	30.8 (±4.5)	-1.02 (-0.891 to 2.936)
weight (Kg)	67.37±8.12	68.19±5.48	0.91 (-4.42 to 11.21)
height, (cm)	158.14 ±4.22	159.12± 4.52	0.72 (-19.8 to 4.74)
BMI	29.1 ± 8.8	29.4 ± 3.3	0.93 (-1.1 to 0.96)
Post anesthesia axillary temperature (°C)	35.9(±0.6)	35.8(±0.5)	0.82 (-0.12 to 0.4)
Durations of surgery (min)	54 (±15)	51 (±18)	3.24 (-3.86 to 10.34)
Duration of anesthesia (min)	119.1 (±26.6)	108.7 (±23.7)	-10.3 (-20.9 to 0.24)
Ambient temperature of operation room (°C)	26.6 (±1.7)	26.5 (±1.5)	-0.14 (-0.88 to 0.59)
Ambient temperature of PACU (°C)	26.7 (±1.9)	27.3 (±1.7)	0.56 (-0.32 to 1.44)
Sensory block level	T4-T6	T4-T6	-

Mean and the standard deviation was presented

Table 2. Incidence, severity, and other timeline related to shivering in the two groups

Outcome	Normal Saline (n=45)	Ketamine (n=45)	Mean differences (95% CI)	*P*
Incidence of Shivering (n, %)	24 (53.3%)	15 (33.3%)	0.62 (0.38 to1.02)	0.08†
The intensity of Shivering (Median, quartile 1-3)	1 (0-2)	0 (0-2)	Not calculated	0.034††
Time interval between SA block with incision (minute)	2.39±0.12	2.4±0.13	0.014 (-0.046 to 0.076)	0.633†††
Time interval between skin incision to delivery (minute)	4.3±0.21	4.35±0.23	0.042 (-0.547 to 0.14)	0.385†††
Time from SA block to administer study drugs (minute)	6.68±0.28	6.64±0.3	-0.043 (-0.17 to 0.85)	0.507†††
Time from spinal anesthesia to beginning of shivering (minute)	33.1 (±11.7)	41.6 (±20.7)	-8.453 (-19.1 to 2.18)	0.116†††

† *Chi*-square test was used for analysis, and relative risk was presented.
†† Mann-Whitney U test was used for analysis.
††† Independent *t*-test was used for data analysis

The incidence of nausea, vomiting, hypotension, and bradycardia was not different between the groups (Table 2). A significantly higher incidence of nystagmus and grades 1 and 2 sedation was observed in the ketamine group when compared with the saline group. Episodes of respiratory depression were not detected in any patient during the study (Table 3).

Table 3. Adverse events in the two groups

Outcome		Normal Saline (n=45)	Ketamine (n=45)	Relative Risk (95% CI)	*P*
Grade of sedation (n, 0/1/2/3/4)		42/3/0/0	3/26/12/4/0	Not calculated	0.001†
Adverse events	**Nausea (n, %)**	12 (26.7%)	18 (40%)	1.3 (0.9 to 2)	0.18††
	Vomiting (n, %)	8 (17.8%)	14 (31.1%)	1.4 (0.9 to 2.1)	0.14††
	Hypotension (n, %)	27 (60%)	25 (55.6%)	0.9 (0.6 to1.3)	0.67††
	Bradycardia (n, %)	3 (6.7%)	0	2.07 (1.6 to 2.5)	0.24†††
	Nystagmus (n, %)	0	16 (36.6%)	2.3 (1.7 to 3.2)	0.0001†††

† Mann-Whitney U test was used for analysis
†† Chi-square test was used for analysis, and relative risk was presented
††† Fisher Exact test was used for analysis, and relative risk was presented

Discussion

In this study, we demonstrated that the administration of i.v. Ketamine 0.3 mg/kg after delivery reduced the intensity, but not the incidence of shivering in patients undergoing CSs under SA. However, administration of ketamine is accompanied by an adverse effect such as nystagmus and sedation.

Kose *et al.*, (9) compared the prophylactic antishivering effect of two doses of ketamine (0.25 and 0.5 mg/kg) with saline in 120 pregnant women undergoing CSs during SA. Unlike us, they did not wait for baby delivery and administered study drugs immediately after completion of the spinal block. In their study, the incidence of shivering was significantly lower in the two ketamine groups than in the saline group, and only 1/30 and 2/30 patients in the ketamine 0.5 and 0.25 groups experienced shivering, respectively. However, in our study, 0.3 mg/kg IV ketamine did not change the incidence of shivering significantly. There are two major differences between our work and that of Kose *et al*., the timing of ketamine administration and the use of forced-air warming during surgery. The timing of ketamine administration may have played a substantial role in the incidence of shivering. The use of active warming has been demonstrated to reduce the incidence of postoperative shivering (11-12) and may have influenced their results too.

Ahmed and Aslam (12) compared the efficacy of prophylactic ketamine (0.5 mg/kg) and ketamine (0.25 mg) plus midazolam (37.5 μg/kg) for the prevention of shivering caused by SA in 100 parturient patients that undergone CSs. The incidence of shivering was significantly lower in the ketamine plus midazolam group (4%) than the ketamine group (18%) (12). Also, these results are inconsistent with our results, and the incidence of shivering in our study was higher than in these studies. The main differences between these studies and our study were that in contrast with our study that includes the assessment of shivering from SA beginning to patient discharge from the recovery room, shivering was evaluated for only the first 15 min of the spinal block and the dose of ketamine was higher in the ketamine alone group in the earlier mentioned study (9).

Recently Girmay *et al*., (13) evaluated the effects of ketamine on incidence and intensity of shivering following spinal anesthesia in CSs patients. Both the incidence and severity of shivering decreased by 0.2 mg prophylactic ketamine. The result of this study is incompatible with our results too.

Honarmand *et al*., (14) compared the effect of prophylactic ketamine 0.5 mg/kg, midazolam 75 mg/kg, a combination of ketamine 0.25 mg/kg and midazolam 37.5 mg/kg, and placebo (saline), in the prevention of shivering, during SA using bupivacaine 15 mg on 120 orthopedic patients. They reported that shivering was observed in 60, 50, 23.3, and 3.3% of saline, midazolam, ketamine, and midazolam/ketamine groups, respectively. The incidence of shivering in ketamine 0.5 mg/kg was the same as our study; however, the incidence of shivering in the saline group was higher. The cause of inconsistency between Honarmand *et al*., (14) study and the current study could be related to the type of surgery. Unlike CSs, in orthopedic surgery, more parts of the body are exposed,

which may cause more heat loss. Dal *et al*., (6) compared the efficacy of low-dose prophylactic ketamine with pethidine or placebo in preventing postoperative shivering during general anesthesia. They found that prophylactic low-dose ketamine was effective in preventing postoperative shivering. Using a higher dose of ketamine, general versus spinal anesthesia, and propofol for induction of anesthesia could help to explain the inconsistency between the present study and Dal *et al*.,. (6) study. Another explanation for the failure of ketamine to reduce the incidence of shivering in the present study is that 0.3 mg/kg ketamine was not sufficient. This dose was chosen because higher doses of ketamine could lead to unwanted side effects such as hallucinations and delirium (14). Though, this single low dose may lead to a mismatch between the duration of effect and assessment period.

In the present study, *i.v.* ketamine reduced the intensity of shivering in women undergoing elective CSs under SAB. Shivering resulted from hypothermia during SA due to some reasons such as redistribution of heat from the core to the peripheral compartment, increased heat loss from the body surfaces because of thermoregulatory vasoconstriction below the level of the spinal block, decreases in the vasoconstriction and shivering thresholds, and is expressed as an involuntary muscle contraction (12). Ketamine, a competitive receptor antagonist NMDA, modulate thermoregulation in various levels (2) and probably control shivering by non-shivering thermogenesis either by influencing the hypothalamus or by the beta-adrenergic effect of norepinephrine.

Our results showed that there were no statistically significant differences in axillary temperature between the two groups. Similarly, no relationship has been shown between axillary temperature and the occurrence of shivering in other studies (15).

The rate of spinal adverse events, such as nausea, vomiting, hypotension, and bradycardia, was not different between the two groups; however, sedation grade using Tsai *et al*.,'s (10) scale was higher in the ketamine group. Nystagmus occurred in 36% of patients of ketamine and group, while there was one patient in the normal saline group who had nystagmus. The difference was statistically significant. Sedation and nystagmus are well-known potential side effects of ketamine (7). Probably, the low dose of ketamine (0.3 mg kg^{-1}) used in our study is the cause of the low incidence of side effects. However, even these low doses of ketamine produce sedation and nystagmus. Sedation but not nystagmus is the advantage during surgery under SA, and the use of pharmacological sedation after taking out the fetus could be beneficial in high-stress level patients (16) because low dose ketamine decreases discomfort associated with immobilization on the operating table (17) and decreases post-operative analgesic recruitment without significant mental side effects' (18).

There are some limitations to the present study. First, there was no reliable thermometer to measure core temperature noninvasively, and it was one of the most important limitations of the study. Tympanic temperature is one of the most reliable sites for measurement of core temperature, and it correlates well with brain temperature (11). Second, the scale was not used for the assessment of nausea, vomiting, and hallucination. Third, ketamine was administered after delivery, which might be the mechanisms that induce shivering, which may already be underway, so treatment may not be as effective as compared to the administration before the spinal was placed. Forth, administration of ketamine after delivery may have potential risks for dysphoria, which could have negatively affected the experience of the mother. It was advisable to have a score to test the experience of the participants. And finally, it is likely that our group size of 45 was inadequate to properly detect the differences in the incidence of shivering or drug complications between groups also because Post Hoc power of the study was 48.3%.

Administration of low dose *i.v.* ketamine (0.3 mg/kg) did not decrease the incidence of shivering; however, it was effective in lowering shivering intensity during CSs under spinal anesthesia. Considering this, side effects, such as nystagmus and sedation, may occur and restrict its effectiveness.

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