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Research Article

Could ephedrine replace meperidine for prevention of shivering in women undergoing Cesarean Section under spinal anesthesia? A randomized study

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KEYWORDS

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Abstract *Purpose:* To compare possible unlabeled effect of ephedrine, as shivering prophylaxis, with meperidine during spinal anesthesia for Cesarean Section.

Methods: After institutional ethical committee approval, 96 parturients scheduled for elective cesarean delivery under spinal anesthesia were randomly allocated according to shivering prophylaxis to receive either 15 mg meperidine (group M, $n = 48$) or 6 mg ephedrine (group E, $n = 48$) intravenously before spinal block. Incidence and intensity of shivering as well as side effects of either drug were assessed.

Results: The incidence shivering in meperidine and ephedrine groups in women undergoing Cesarean Section under spinal anesthesia was comparable (27%, 29% respectively, $P = 0.06$). Also, intensity of shivering was not different between two groups. Moreover, phenylephrine requirement and incidence of nausea and vomiting were significantly less in ephedrine group ($121 \pm 2.2\%$ and 4.1% respectively) relative to meperidine group ($168 \pm 3.2\%$ and 16.6% respectively).

Conclusion: The prophylactic use of a low dose ephedrine is effective as meperidine for shivering prophylaxis in women undergoing Cesarean Section under spinal anesthesia as meperidine. Moreover, it is associated with less hypotension, nausea and vomiting.

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1. Introduction

Shivering, rhythmic oscillatory movement of upper limbs, neck and jaw, is common during regional anesthesia with an incidence up to 56.7% of patients [1,2]. Increase of oxygen consumption, CO₂ production, and interference with monitoring of blood pressure and ECG, and general discomfort are the main squeals of shivering [3]. Those effects are particularly bothering in the obstetrical population [4]. Ephedrine, a

well-known sympathomimetic agent, has been used to treat hypotension during regional anesthesia. It has antiemetic effect for short-term [5]. Ephedrine maintained hemodynamics and minimized decrease of the core temperature when given by an intravenous infusion during spine surgery under general anesthesia [6].

Although, meperidine is the best studied drug in the treatment of post-anesthetic shivering, other drugs, like Ondansetron, hydrocortisone, tramadol hydrochloride and nalbuphine were used [7–9]. Side effects of IV meperidine like nausea, vomiting, pruritus, hypotension, bronchospasm, bradycardia, and respiratory insufficiency are reported to be dose-related [10].

The primary concern of this study is to compare effect of a preemptive low dose ephedrine, commonly used during spinal anesthesia for CS, for shivering prophylaxis in women undergoing cesarean delivery under regional anesthesia in comparison with meperidine. Secondary outcome measures were side effects and patients satisfaction.

2. Patient and methods

After institutional ethical committee approval and written informed consent from the parturients, this study was performed in 96 women ASA I and II (American Society of Anesthesiologists), with uncomplicated pregnancies, who were scheduled for elective cesarean delivery under spinal anesthesia.

Exclusion criteria included refusal or contraindications to regional anesthesia or obesity, diabetes or thyroid disease. All parturients received 15 ml/kg IV lactated Ringer's solution over 30 min before spinal injection. The operative room temperature was kept at 21 °C. The parturients were randomly divided into two groups according to shivering prophylaxis using a computer-generated code. The group M ($n = 48$) received i.v. 15 mg meperidine, while group E ($n = 48$) received i.v. 6 mg ephedrine. Both drugs solutions looked identical, were prepared in 2 ml saline by pharmacist unaware of the randomization code and were given by an assistant, who was blinded to group assignment, just before spinal anesthesia. After placement of standard monitors, spinal anesthesia with 0.5% hyperbaric bupivacaine according to height (2.6 ml for patients taller than 155 cm and 2.4 ml for those shorter than 155 cm) was administered. After induction of spinal anesthesia, the parturient was placed supine with left uterine displacement and head up with slight trendelenberg of the table to achieve adequate surgical block (T4 sensory level) which was assessed by analgesia to pinprick with fine dental needle. Non-invasive arterial blood pressure was measured every 5 min until the end of surgery. Supplementary oxygen 3 l/min was administered. Shell temperature was monitored continuously during surgery by means of axillary probe and was reported at 10 min interval. Surface skin warming was achieved by adequate wrapping of the skin. Maternal hypotension (decrease in systolic blood pressure of > 10% from baseline) after spinal anesthesia was treated aggressively with additional IV fluid, more uterine tilt, and increments of IV phenylephrine 25 µg. After delivery of the baby, 5 U of IV oxytocin was given to all parturient to enhance uterine contraction. Intensity of shivering was assessed using a five-point scale: Grade 0: No shivering; 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 [11]. Shivering was assessed at every 5 min for 1 h after spinal anesthesia then at 80 and 90 min later.

An ant shivering “rescue” drug (4 mg ondansetron intravenously) was administered in case of need for shivering treatment within the study period.

Data were also collected regarding time the durations of surgery, amount of phenylephrine consumed and complications (nausea, vomiting, pruritus, respiratory depression and allergic reactions). Patient satisfaction with shivering prophylaxis was evaluated and recorded (11-point verbal numeric scoring system, 0 = not at all satisfied, 10 = fully satisfied). Sedation was assessed with modified Ramsey sedation score (RSS) [12] (Awake levels were: 1, patient anxious and agitated or restless or both; 2, patient co-operative, orientated, and tranquil; 3, patient responds to commands only. Asleep levels were dependent on the patient's response to a light glabellar tap or loud auditory stimulus: Level 4, a brisk response; 5, a sluggish response; and 6, no response) 20 min after spinal block.

3. Statistical analysis

The statistical analysis of data was done by using excel program and SPSS program (statistical package for social science) version 11 (SPSS Inc., Chicago, IL, USA). K–S (Kolmogorov–Smirnov) test was done to test the normality of quantitative data. The analysis of the data was done using Student's unpaired *t*-test. Scores for pain and sedation were analyzed using the Mann–Whitney U-test. Data were expressed as mean ± standard deviation or frequency (%), or medians (ranges). *P* is significant if < 0.05 at confidence interval 95%. Sample size was determined by using Epicalc program 2000 at power 80% and confidence interval 95% assuming that the highest shivering intensity score was 85% [4]. To find a 50% reduction of that value, a sample size of 40 patients per group was necessary. Extra numbers were taken to avoid defaulters, so each group = 50.

4. Results

One hundred and three parturients were assessed for eligibility. Three patients were excluded; two with hepatic insufficiency and one with localized infection at site of spinal anesthesia. One hundred parturients were randomized into two equal groups. Two cases were excluded in either group (Figure 1). The two groups were not significantly different with respect to demographic characteristics (Table 1). The two groups were statistically comparable as regard to heart rate and mean arterial blood pressure (Figures 2 and 3).

The two groups showed no difference regarding level of sensory block, duration of surgery and sedation score. However, total dose of phenylephrine was significantly less in group E. Number of patients who experienced shivering or requiring additional anti-shivering rescue was comparable in both groups. Also, intraoperative temperature of both groups were comparable at different time points (Table 2). Grading of shivering showed no statistically significant difference between two groups (Figure 4). Nausea and vomiting were statistically significant less in group E when compared to group M. Satisfaction score was comparable in both groups (Table 3).

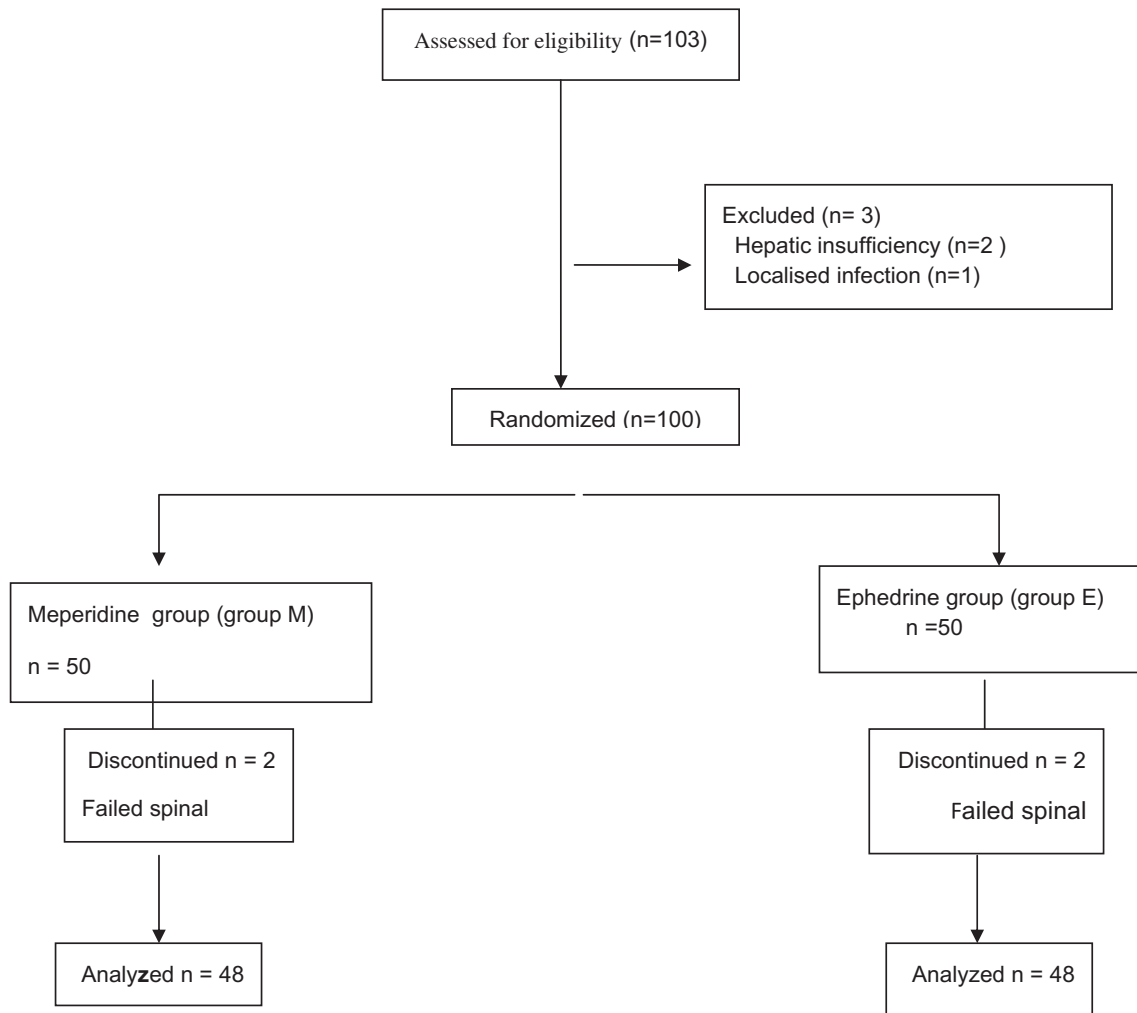


Figure 1 Study flowchart.

Table 1 Demographic data of patients.

Variable	M group (n = 48)	E group (n = 48)	P value
Age (yr)	28.5 ± 2.4	27.8 ± 4.3	0.43
Weight (kg)	81 ± 2.4	79 ± 3.2	0.51
Height (cm)	168.2 ± 3.4	168.3 ± 3.3	0.42
Gestational age (weeks)	38.6 ± 1.4	38.7 ± 3.1	0.5

M; meperidine, E; ephedrine. Data are presented as mean ± standard deviation.
* P < 0.05 significant compared with group M.

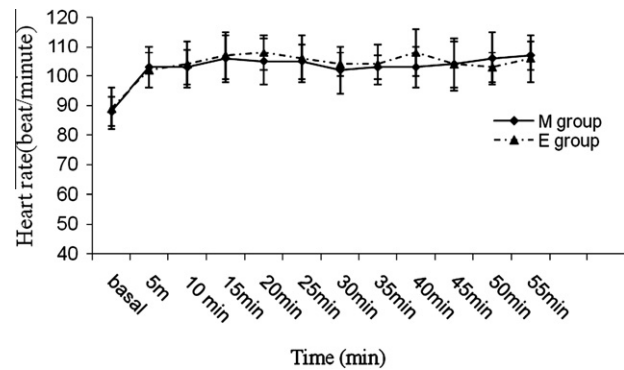


Figure 2 Intraoperative heart rate changes (beat/min).

5. Discussion

This study showed that use a small dose of ephedrine, as shivering prophylaxis in women undergoing Cesarean Section under spinal anesthesia, resulted in similar incidence (29% compared to 27%, P = 0.06) and intensity of shivering as meperidine. Furthermore, it is associated with less hypotension, as evidenced by less phenylephrine requirement (121 ± 2.2 versus 168 ± 3.2, P value = 0.04), nausea and

vomiting (16.6 versus 4.1%, P value = 0.03) and comparable satisfaction with shivering prophylaxis.

Meperidine has been given by intrathecal route to reduce the incidence and severity of shivering during spinal anesthesia for CS [4]. Intravenous meperidine, in a dose of 25 mg, is the gold standard for the treatment of post-anesthetic shivering as it can stop it within 5 min [13,14]. The use IV meperidine

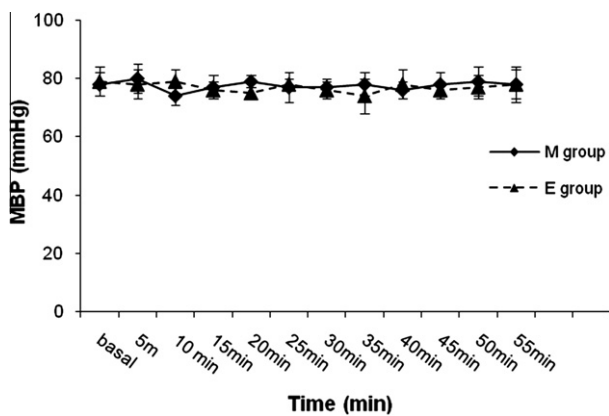


Figure 3 Intraoperative mean blood pressure changes (mm Hg).

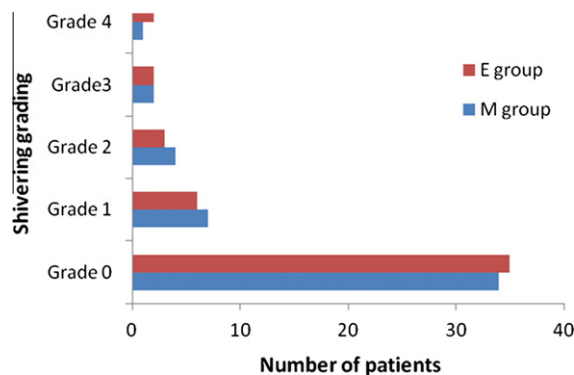


Figure 4 Intensity of shivering.

for prophylaxis against shivering spared the patients from negative experience associated with shivering and resulted in less side effects associated with meperidine [4]. Anti-shivering of meperidine is mediated by κ -receptor agonist activity [15,16].

Ephedrine, a well-known sympathomimetic agent, is frequently used for treatment of hypotension especially during CS under spinal anesthesia [17]. Ephedrine has been reported to have antiemetic effects during laparoscopic cholecystectomy, abdominal hysterectomy and gynecologic laparoscopy [18–21]. The exact mechanism of unlabeled shivering prophylaxis achieved by low dose ephedrine under spinal anesthesia is unknown. It could be explained by vasoconstriction of skeletal muscle vessels which could counteract loss of thermoregulatory vasoconstriction below the level of spinal blockade. Ephedrine has been investigated to minimize the decrease of the core temperature during spine surgery under general anesthesia. Jo et al. [6] concluded that maintenance of the core temperature by ephedrine is primarily due to enhancing the sympathetic neuronal release of norepinephrine and epinephrine, which is mediated through beta-adrenoreceptors stimulation. Correlation between core and surface temperatures during shivering prophylaxis with ephedrine or meperidine has been extensively discussed [6,7,22,23] so it is not investigated in this study. In this study, we use a fairly low dose of either drug to avoid complications.

Table 3 Patient satisfaction and side effects.

Variable	M group (n = 48)	E group (n = 48)	P value
Patient satisfaction score	8.6 ± 1.2	8.7 ± 1.3	0.4
Nausea and vomiting (%)	8 (16.6%)	2 (4.1%)*	0.03
Pruritus (%)	1 (2%)	1 (2%)	0.13
Respiratory depression (%)	0	0	

Data are presented as mean ± standard deviation or number (%). * P < 0.05 significant compared with group M.

To date, no studies discuss use of ephedrine as shivering prophylaxis during CS under spinal anesthesia.

In this study, phenylephrine was used to keep blood pressure within 10% from baseline value, so that the difference in consumed phenylephrine (121 ± 2.2 in E group versus 168 ± 3.2 in M group, P value = 0.04) can be attributed to use of ephedrine.

Limitations to this study include absence of a placebo control group as it would be non-ethical to include such a group to identify the documented anti-shivering effect of the used drug. Another limitation is that we did not record esophageal core temperature as ephedrine was concluded, in a previous study to prevent decrease of the core temperature during spine

Table 2 Intraoperative data.

Variable	M group (n = 48)	E group (n = 48)	P value
Sensory block (median, range)	T4 (T2–T6)	T4 (T2–T5)	0.34
Surgery duration (min)	56.2 ± 1.7	55.3 ± 2.2	0.6
Phenylephrine dose (µg)	168 ± 3.2	121 ± 2.2*	0.04
Shivering (%)	13 (27%)	14 (29%)	0.06
<i>Intraoperative temperature (°C)</i>			
10 min	34.3 ± 1.3	34.1 ± 1.2	0.52
20 min	33.3 ± 1.4	32.5 ± 1.3	0.41
30 min	32.1 ± 1.3	31.6 ± 1.4	0.43
40 min	32.1 ± 2.1	31.3 ± 1.6	0.44
50 min	32.6 ± 2.2	31.4 ± 1.9	0.45
Rescue anti-shivering (%)	3 (6.25%)	4 (8.3%)	0.06
Sedation score	0 (0–1)	0 (0–0)	0.23

Data are presented as mean ± standard deviation or number of patient (percentage of study group) or median (range).

* P < 0.05 significant compared with group M.

surgery under general anesthesia. Moreover, the primary concern of this study is to compare two anti-shivering drugs.

Further studies are needed to optimize the dose of ephedrine as shivering prophylaxis in women undergoing Cesarean Section under spinal anesthesia.

In summary, a low dose ephedrine reduced the incidence and intensity of shivering in women undergoing Cesarean Section under spinal anesthesia as meperidine. Moreover; it is associated with less hypotension, nausea and vomiting and comparable patient satisfaction.

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