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Comparison of the Effects of Intrathecal Meperidine and Morphine on Incidence and Intensity of Shivering After Caesarean Sections Under Spinal Anesthesia: A Randomized Controlled Trial

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Abstract

Background: Shivering is a common unpleasant problem in parturients undergoing cesarean section under spinal anesthesia. Therefore, attempts for solving this problem are rational.
Objectives: To evaluate and compare the effect of intrathecal meperidine with morphine on the incidence and intensity of shivering and other side-effects during delivery under spinal anesthesia.
Methods: In a double blind randomized controlled trial, 90 parturient women who were scheduled for elective cesarean delivery under spinal anesthesia were selected conveniently and randomly divided in 3 groups at the Besat hospital, which is a tertiary referral hospital in Sanandaj, Iran, from March to October 2013. Spinal anesthesia was applied using 12.5 mg of hyperbaric bupivacaine 0.5% combined with 10 mg meperidine in group P (n = 30), 12.5 mg of hyperbaric bupivacaine 0.5% combined with 0.2 mg morphine in group M (n = 30), and 12.5 mg of hyperbaric bupivacaine 0.5% combined with 0.5 mL saline in group S (n = 30).
Results: Incidence of shivering in the meperidine group (6.7%) was significantly lower than the morphine (40%) and control groups (67.7%, P = 0.0001). The intensity of shivering in the meperidine group (0.13) was significantly lower than the morphine (0.73) and control groups (1.43, P = 0.001). There was no clinically significant difference in anesthesia's side effects between the 3 groups.
Conclusions: According to the study results, adding either meperidine or morphine to hyperbaric bupivacaine during spinal anesthesia for cesarean section decreases the incidence and severity of shivering without increasing the side effects. However, intrathechal meperidine is superior for this purpose.

Keywords: Cesarean Section, Spinal Anesthesia, Shivering, Intrathecal, Morphine, Meperidine

1. Background

Due to many advantages of neuraxial anesthesia for both mother and neonates, in comparison with general anesthesia, it is a more preferred method for cesarean delivery (1), however it causes impairment in the thermoregulatory function of the autonomic system and results in shivering (2, 3).

Although the reported incidence of shivering varies depending on the study, it is estimated to occur in up to 50% of patients undergoing cesarean delivery under spinal anesthesia (4). Perioperative shivering leads to patient uneasiness, more postoperative bleeding, higher blood pressure, tachycardia, more oxygen consumption, more carbon dioxide production, increased metabolic rate by fourfold, and may disturb the functioning of monitoring devices during anesthesia (5, 6).

One of the known effects of intrathechal opioids is the prevention and treatment of postoperative shivering (3, 5, 7). However, the safety of this practice is not completely stabilized. Roy et al. suggested that combined intrathecal meperidine and morphine reduced the incidence as well as intensity of shivering associated with intrathecal anesthesia for cesarean delivery without increasing side effects (8). On the other hand, Khan et al. (9) rejected the use of intrathecal meperidine because of increased incidence of nausea and vomiting. This controversy about usefulness and side effects of intrathecal meperidine or morphine is continued in other studies (10-13), which makes it necessary to conduct further studies.

The objective of this double-blinded randomized controlled trial was to evaluate and compare the effect of intrathecal meperidine with morphine on the incidence and severity of shivering after cesarean section (CSs) and to determine their side effects.

2. Methods

2.1. Design

This study was a double blind randomized controlled trial, which was conducted after receiving approval from the ethics committee of Kurdistan University of Medical Sciences and was registered at the Iranian registry of clinical trial database (IRCT2013091414656N1). This study was performed according to the requirements of the declaration of Helsinki. The sampling frame included patients who were scheduled for elective CSs under spinal anesthesia at the Besat hospital, a governmental, tertiary referral hospital in Sanandaj, Iran, and were enrolled in this study from March 2013 to October 2013. The sampling method was a convenient method that was done up to complete the sample size.

The inclusion criteria were American Society of Anesthesiologists physical status I-II, pregnant women in their 37th - 41st weeks of pregnancy, and aged from 18 to 40 years. Patients with contraindications to regional anesthesia, cardiovascular diseases, twin or more pregnancy, fever, hypo or hyperthyroidism, hypersensitivity to study drugs, BMI > 30, and history of headache were excluded. Furthermore, during the study period, patients with a massive hemorrhage requiring transfusion, insufficient block level, and/or need for additional rescue analgesics during surgery were excluded from the study.

After obtaining written informed consents, patients were randomly divided into 3 groups' of meperidine, morphine, and saline by simple randomization using the Random Allocation Software version 1 (Isfahan University of Medical Sciences, Isfahan, Iran). Randomization was conducted by a trained anesthetic and this person was removed from the rest of the study.

2.2. Intervention

The saline group received 12.5 mg (2.5 mL) of hyperbaric bupivacaine 0.5% (Marcaine, AstraZeneca, Sweden) plus normal saline (0.5 mL). Intervention groups received the same dose of hyperbaric bupivacaine 0.5% combined with 10 mg (0.2 mL) meperidine (Hana Pharmaceutical Corp, Korea) or 0.2 mg (0.2 mL) morphine (Morphine sulfate DP, Aburaihan LTD, Iran) and normal saline (0.3 mL). The medications were prepared by an anesthetic nurse.

All patients fasted for at least 8 hours. Before performing the spinal anesthesia, a 20G venous catheter was inserted into the forearm vein and patients received intravenous preheated (37°C) lactated ringer's solution 10 mL/kg. Patients were placed under monitoring for oxygen saturation, blood pressure, heart rate, electrocardiogram, and axillary temperature.

Patients were placed in an upright sitting position and spinal anesthesia was performed at the L3 - L4 or L4 - L5 interspaces through a midline approach using a 25G Quincke needle. Immediately, the patients were placed in the supine position with a left displacement of uterine, the level of sensory block was evaluated by an alcohol-soaked cotton before the start of surgery, and the maximum height of the sensory block was recorded.

Supplemental oxygen 5 Liter/minute was administered through a simple face mask during anesthesia and recovery time. During the operation, the operating room temperature was maintained at 24 - 26°C using a room temperature control system; all intravenous fluids were warmed up to 37°C, and the patients were covered with one layer of surgical drapes, which covered the whole body except the head and neck during the operation. In addition, one simple cotton blanket was used in the post anesthesia care unit (PACU), while no active warming was utilized.

2.3. Assessment Tools

The demographic data, amount of hemoglobin and hematocrit (before and 8 hours after surgery), duration of surgery (duration from skin opening to suturing), duration of anesthesia, ambient temperature of operative room and PACU, as well as anesthesia side-effects (hypotension, bradycardia, respiratory depression, nausea, vomiting, and pruritus) were recorded. A blind investigator recorded the incidence and intensity of shivering and complications at 5-minute intervals during the operation and every 15 minutes in the PACU.

Three aspect of shivering including; shivering incidence, shivering time (time from initiation of anesthesia to beginning of shivering), and shivering score were assessed. Shivering score was graded on a 4 point scale: "zero = no shivering, 1 = shivering in face or neck, 2 = muscular activity in more than one muscle group, but not generalized, and 3 = shivering involving the whole body" (14) Shivering ranked greater than 2 was treated by 30 mg intravenous (IV) meperidine, hypotension by 5 - 10 mg IV ephedrine, bradycardia by 0.5 mg IV atropine, and nausea or vomiting by 4 mg IV ondansetron.

2.4. Statistical Methods

2.4.1. Sample Size Estimation

To obtain a minimum of 30% reduction in the incidence of shivering in the study groups in comparison to the control group (considering shivering rate of 50% in the placebo group and 20% in the study groups), with α error of 0.05 and power of 80%, the sample size was calculated so that there was at least 29 patients in each group.

2.4.2. Data Analysis

Analysis was done as per-protocol analysis. SPSS version 16 was used for data analysis. Quantitative variables with normal and non-normal distribution were compared using the Anova test as well as Kruskal-Wallis test, respectively. Side effects were analyzed using Chi-square test, when appropriate. The intensity of shivering was compared using Kruskal-Wallis test. Data were explained as mean ± SD, median (quartile 1, quartile 3), and numbers or percentages, as appropriate. P value of < 0.05 was considered statistically significant.

3. Results

From the 116 patients who were included in the study, 95 were randomized in 3 groups, from whom 5 were excluded, and data of 90 were analyzed (Figure 1). There were no differences between the groups with regards to the patient's age. The operation time, anesthesia duration, and ambient temperature were also similar in the 3 groups (Table 1).

Shivering time, maximum sensory block level, and 24-hour post-operative hemoglobin and hematocrit were also similar in the 3 groups (Table 1). Following spinal anesthesia, shivering was observed in 23 (67.7%) patients from the control group, 12 (40%) in the morphine group, and 2 (6.7%) in the meperidine group ($P < 0.001$). The mean intensity of shivering in the control, morphine, and meperidine groups were 1.47 (± 1.07), 0.73 (± 1.01), and 0.13 (± 0.5), respectively ($P < 0.001$). The data regarding shivering time and time of shivering occurrence after spinal anesthesia are presented in Table 2.

The occurrence of other side effects including hypotension, bradycardia, nausea, and vomiting showed no difference between the groups (Table 3). None of the patients in the 3 groups had pruritus or clinically significant respiratory depression.

4. Discussion

The results of this study showed that adding either meperidine 10 mg or morphine 0.2 mg to 12.5 mg hyperbaric bupivacaine for spinal anesthesia significantly reduced the incidence and intensity of shivering after cesarean delivery. However, the meperidine is more effective than morphine for this purpose.

Shivering is a fluctuating and involuntary contraction of the skeletal muscle, with potential increasing discomfort in patients (14). The etiology of shivering under regional anesthesia is still obscure, however some of the proposed likely hypotheses are as followed; redistribution of internal body temperature produced by vasodilatation under the level of block, failure of thermoregulatory vasoconstriction under the level of blockade area that could intensify heat loss from the body surface due to the extreme thermo genesis, and lessening of vasoconstriction threshold and simultaneously mild increase in the sweat threshold (15, 16).

Anti-shivering effect of IV meperidine is well known, so that intravenous infusion of meperidine is considered as the gold standard for treatment of shivering (3, 17). Presumably this feature of meperidine is mediated by activating a kapa-opioid receptor, anticholinergic action, inhibition of biogenic monoamine reuptake, antagonism of N-Methyl-D-aspartate receptor (NMDAR), and stimulation of α2-adrenoceptors (18, 19). Unlike intravenous meperidine, there are no consensus regarding mechanism and effectiveness of intrathechal meperidine on post spinal anesthesia shivering.

Morphine is another opioid that had been used most commonly as an adjutant to intrathecally administered local anesthetics for pain control after cesarean delivery (20). There is more doubt regarding the anti-shivering effect of intrathechal morphine in comparison to meperidine.

Roy et al. (8) compared the anti-shivering effect of intrathecal meperidine 0.2 mg/kg and morphine 0.15 mg with morphine 0.15 mg alone. They concluded that the administration of prophylactic intrathecal meperidine for caesarean delivery is more effective than morphine in reducing the incidence and severity of shivering.

In another study, Hong et al. (21) compared the anti-shivering effect of different doses of morphine (0.1 mg or 0.2 mg) with meperidine (10 mg) when added to intrathecal bupivacaine (8 - 10 mg) during elective cesarean delivery under combined-spinal epidural anesthesia. The incidences of shivering were 17%, 13.3%, and 3.3% in the groups receiving 0.1 mg morphine, 0.2 mg morphine, and 10 mg meperidine, respectively. They concluded that the fixed dose of intrathecal meperidine 10 mg was more effective than morphine in reducing the incidence and intensity of shivering. Results of our study are in agreement with the data found in these 2 previous mentioned studies. In the study done by Khan et al. (9), 12.5 and 25 mg of intrathechal meperidine were compared to evaluate their effects on shivering. Both doses of meperidine were effective in decreasing shivering. However, owing to increasing incidence of nausea/vomiting they concluded that they do not agree with intrathecal meperdine. Results of the current study is in agreement with Khan et al. (9) in terms of shivering, however, the incidence of nausea/vomiting was not higher in the 2 studies groups in comparison to the control group in our study. The reason of this discrepancy between 2 studies is related to the dose of meperdine, we

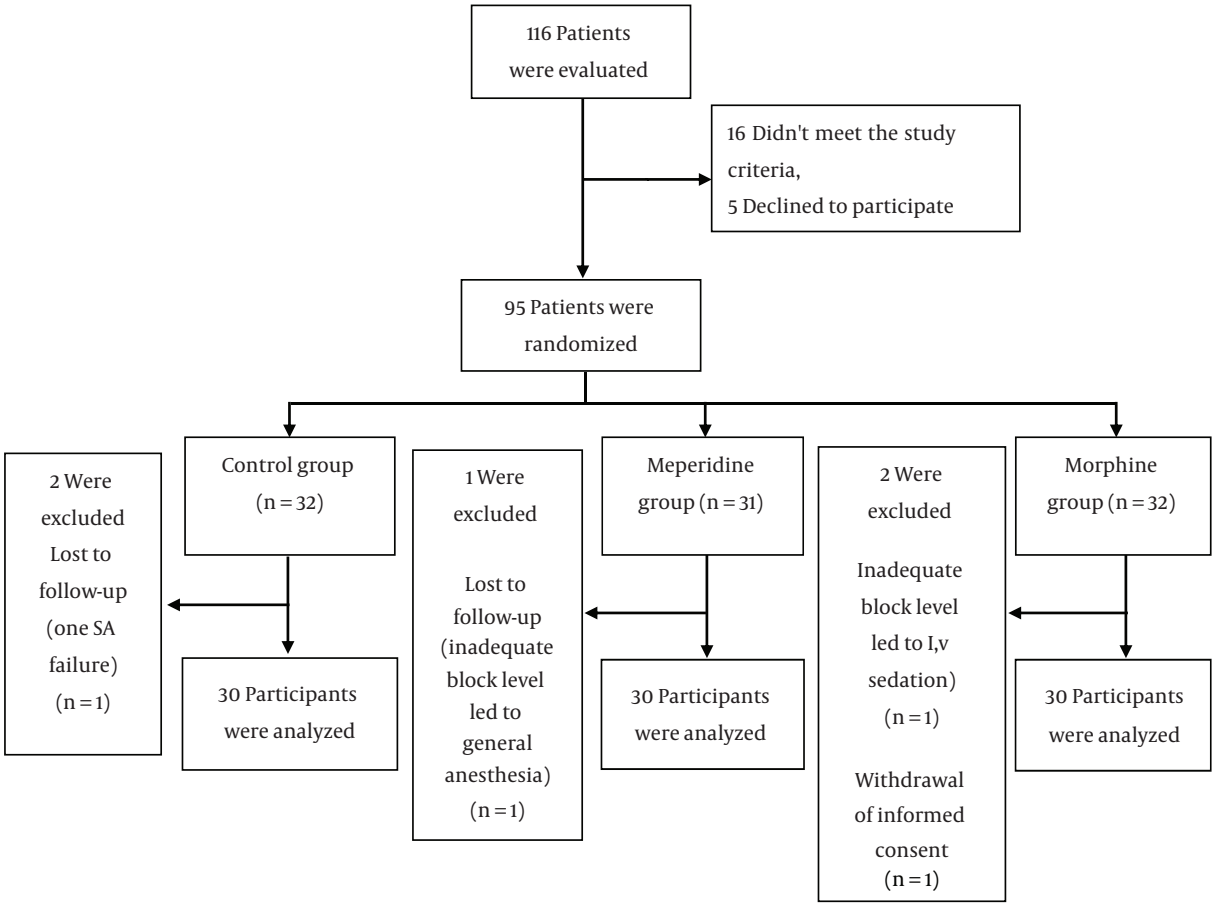

Figure 1. Profile of the Participants of the Study

Table 1. Comparison of Basic and Following Surgery Variables Between the Three Groups (N = 30)[a]

Variables	Control	Meperidine	Morphine	P Value
Age, y	29.8 ± 5.3	29.4 ± 6.02	30 ± 6.1	0.906[b]
Base Hb, , mg/dL	12.4 ± 1.05	12.4 ± 0.95	12.2 ± 0.84	0.37[b]
After 8 hours Hb, mg/dL	11.8 ± 1.2	12.6 ± 0.96	11.3 ± 1.3	0.17[b]
Base Hct, %	37 ± 2.8	37.2 ± 2.8	37.3 ± 2.8	0.67[b]
After 8 hours Hct, mg/dL	35.5 ± 2.5	36.4 ± 2.6	34.7 ± 3.3	0.3[b]
Durations of surgery, min	54.8 ± 14	50.1 ± 18	48.8 ± 17.7	0.374[b]
Duration of anesthesia, min	115.6 ± 25	119.3 ± 20.9	97.7 ± 28.4	0.002[b]
Ambient temperature of operation room, °C	26.2 ± 1.3	26.9 ± 1.3	27 ± 1.2	0.044[b]
Ambient temperature of PACU, Median (quartile 1 - quartile 3), °C	27.1 (27 - 28)	28 (27 - 29)	28 (27.9 - 28.33)	0.024[c]

Abbreviations: Hb, Hemoglobin; Hct, Hematocrit.
[a]Values are expressed as mean ± SD.
[b]ANOVA test was used for data analysis.
[c]Non normal distribution, Kruskal-Wallis Test was used for data analysis.

Table 2. Comparison of Incidence and Intensity of Shivering Between the Three Groups (N = 30)

Shivering	Control	Meperidine	Morphine	P Value
Intensity score of shivering, Median (quartile 1 - quartile 3)	1.5 (0.75 - 2)	0 (0 - 0)	0 (0 - 2)	< 0.001[a]
Shivering incidence, No (%)	23 (76.7)	2 (6.7)	12 (40)	< 0.001[b]
Shivering score, No. (%)				< 0.001[a]
0	12 (40)	28 (93.3)	18 (60)	
1	3 (10)	0	4 (13.3)	
2	9 (30)	2 (6.7)	6 (20)	
3	6 (20)	0	2 (6.7)	
Shivering incidence time, Median (quartile 1 - quartile 3), min	30 (30 - 30)	52.5 (40 - 65)	17.5 (10 - 60)	0.284[a]
Shivering duration, Median (quartile 1 - quartile 3), min	2 (1 - 3)	3 (2.5 - 3)	2 (1 - 3)	0.487[a]

[a] Non normal distribution, Kruskal Wallis test was used for analysis.
[b] Chi-square test was used for analysis.

Table 3. Comparison of Incidence of Side Effects Between the Three Groups (N = 30)[a,b]

Side Effects	Control	Meperidine	Morphine	P value
Nausea	10 (33.3)	12 (40)	8 (26.7)	0.54
Vomiting	5 (16.7)	6 (20)	5 (16.7)	0.927
Hypotension	21 (70)	20 (66.7)	23 (76.7%)	0.685
Bradycardia	0 (0)	5 (16.7)	4 (13.3)	0.075

[a] Values are expressed as No. (%).
[b] Chi-square test was used for analysis.

used 10 mg intrathecal meperidine, which is less than the dose used in the above study, which could be the reason for a lower adverse effect of intrathecal meperdine.

Meperidine is a synthetic compound of morphine and has a same affinity to MU, Kappa, and Delta opioid receptors (22). In contrast to meperidine, morphine has a low efficacy in prevention of shivering. As a hypothesis, a lower anti-shivering effect of morphine may be related to its low lipid solubility. It is possible that the process of shivering following spinal anesthesia begun immediately after subarachnoid administration of local anesthetics and before the beginning of morphine effect. Therefore, one could attribute the differences between intrathecal meperidine and morphine to this issue.

Results of current study showed that intrathecal meperidine as well as morphine did not increase the side effects in comparison with the control group. Khan et al. (9) found an association between the increased incidence of nausea and vomiting by adding meperidine to subarachnoid administered bupivacaine, and also by higher doses of intrathecal meperidine (25 mg) in comparison to a lesser dose (12.5 mg). Bhukal et al. (13) showed that the incidence of shivering was lower in the meperidine 0.5 mg/kg

than 0.3 mg/kg but none of these doses of meperidine had a statistically significant adverse effect on patients, compared with placebo. Results of these aforementioned studies are in contrast with our results. We used the lower doses of meperidine (10 mg) in comparison with these studies, which can justify the differences between the results. Nausea, vomiting, pruritus, drowsiness, hypotension, bronchospasm, bradycardia, and respiratory depression have been reported as side effects of intravenous meperidine (17).

The current study had some limitation. Firstly, we monitored axillary temperature instead of core body temperature. The axillary temperature, however, may be used to measure the core temperature, except for extreme body temperature changes (16). Secondly, study registration was done retrospectively. Thirdly the amount of added normal saline to bupivacaine was different between the studies and the control groups. It may change the baricity of administered drugs in the 3 groups and incidentally influence the results. Finally we did not evaluate and compare some demographic characteristics of patients such as height, weight, and BMI.

4.1. Conclusion

According to the study results, the addition of either 10 mg meperidine or 0.2 mg morphine to 12.5 mg 0.5% hyperbaric bupivacaine during spinal anesthesia for cesarean section decreases the incidence and severity of shivering without increasing side effects. However, intrathechal meperidine is superior for this purpose.

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Footnote

Conflict of Interests: We declare any conflicts of interest.

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