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Antishivering Effect of Low Dose Meperidine in Caesarean Section under Spinal Anesthesia: A Randomized Double-blind Placebo-controlled Trial

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Abstract: Shivering related to spinal anesthesia is a usual complication. This study was designed to evaluate the anti-shivering effect of small intrathecal dose of meperidine on the incidence and intensity of shivering in parturient with caesarean section under spinal anesthesia. Seventy parturient, American Society of Anesthesiologists (ASA) physical status I to II, scheduled for elective caesarean section under spinal anesthesia were enrolled in two groups. The parturient were randomized to receive 10 mg bupivacaine 0.5% and 10 mg meperidine (group BM, n = 35) or placebo (10 mg bupivacaine 0.5% and normal saline, group B, n = 35) 3 min after spinal puncture. Demographic values, surgery data, adverse events and the mean intensity for each parturient were assessed during the whole time of study period by a blinded observer. The incidence of shivering during the whole time of the study period was significantly decreased in the group of parturient who received intrathecal meperidine ($p < 0.001$). There were no significant differences in the other measured variables. These findings indicate that using single-shot, mini-dose intrathecal Meperidine (10 mg) reduces the severity and intensity of intra- and post-operative shivering in caesarean section under spinal anesthesia without increasing adverse events.

Key words: Caesarean, intrathecal meperidine, shivering, spinal anesthesia

INTRODUCTION

Shivering occurs in response to sympatholysis, vasodilatation and increased heat loss. Shivering related to spinal anesthesia is a usual complication and reason of this unusual muscular activity is still unknown (Crowley and Buggy, 2008). The incidence range of shivering was variable from 36-55% in different studies (Chun *et al.*, 2010; Locks, 2012; Khaw *et al.*, 2006). Intraoperative shivering is inhibited during general anesthesia; accordingly they are more prone to hypothermia and post-operative shivering. Hence, there are two important elements to regional anesthesia-induced shivering: (1) The desired effect of shivering and (2) The unwanted effects of shivering (Bhukal *et al.*, 2011). Shivering increases cardiac output and causes tachycardia, also hypothermia-induced shivering causes hypoxemia and increases total body oxygen consumption. Those effects are bothersome in mothers and her fetus during delivery (Locks, 2012). Due to the spinal anesthesia advantages including rapid onset, minimal fetal and maternal drug exposure and high success rate it is a

popular technique for cesarean section (Khaw *et al.*, 2006). Shivering related to spinal and epidural anesthesia is distressing for parturient that it may cause cardiovascular and metabolic disturbance. There is little known about the best way of prevention of shivering during spinal anesthesia (Crossley, 1992).

There are many drugs that have been used to treat per anesthetic shivering, including meperidine, ketanserin, doxapram and clonidine and many studies have showed that meperidine is extremely more effective in treating shivering than others (Kranke *et al.*, 2002, 2004). Combined spinal-epidural block is more sufficient than epidural block because its efficacy and fewer side effects (Karaman *et al.*, 2005). Meperidin is an opioid drug with known anti-shivering effect but with their dose-dependant property adverse events such as hemodynamic effects, nausea and vomiting. The antishivering effect of meperidine is referred to its role in reducing the shivering threshold owing to its effect on kappa opioid receptor and on α_{2b} adrenoreceptor subtype (Khan *et al.*, 2011).

During last decade, some studies reported positive effects of different doses of intrathecal meperidine during spinal anesthesia on reducing severity and incidence of perioperative shivering (Fukuda, 2005; Casey *et al.*, 1988; Chen *et al.*, 1993). Intra venous meperidine widely is used for treatment shivering intraoperative (during the caesarean section) and post operative (in recovery room) but it could be associated with side effects. Alternatively, high dose using of intrathecal meperidine may have similar side effects such as nausea, vomiting, respiratory distress and pruritus. Adding meperidine to the intrathecal hyperbaric bupivacaine fusion during spinal anesthesia reduces the incidence and severity of shivering that was done on obstetrical populations undergoing caesarean delivery (Roy *et al.*, 2004; Hong and Lee, 2005).

Different doses of intrathecal meperidine have been used to prevent shivering during spinal anesthesia (Khan *et al.*, 2011; Chen *et al.*, 1993; Roy *et al.*, 2004; Hong and Lee, 2005; Karamaz *et al.*, 2003). There is controversy between different studies in concerning the best dose of meperidine for prevention of shivering. Using single-shot intrathecal meperidine may be useful for reducing intra- and post-operative shivering of parturient and it may be associated with fewer side effects. The preventive effect of a low dose of intrathecal meperidine (10 mg) on shivering has never been studied. The present study is performed to determine that single-shot, mini-dose intrathecal meperidine is effective in reducing the incidence and intensity of perioperative shivering in women with cesarean section.

MATERIALS AND METHODS

Patients: This was a randomized double-blind placebo-controlled trial study being performed in Peymaniyeh and Motahari Hospitals, two healthcare centers affiliated with Jahrom University of Medical Sciences between October 2012 and November 2012. One hundred parturients were considered for eligibility and after describing the study protocol, an informed consent was taken from the patients. Seventy parturients [American Society of Anesthesiologists (ASA) physical status I or II] scheduled for elective caesarean delivery under spinal anesthesia were enrolled (Fig. 1). Parturients with history of sever preeclampsia, contraindication to spinal anesthesia and caesarean section surgery excluded from study. Diabetes, preoperative body temperature $>38^{\circ}\text{C}$, allergy to the study medications (meperidine and bupivacaine), ASA III and IV, drug addiction, a height <152 cm, Reynaud's syndrome and hypo or hyperthyroidism are other exclusion criteria. Parturients with BMI >25 or <19 were excluded.

Intervention: Parturients were randomly divided into 2 groups by random drawing of sealed envelopes (computer-based table of randomization). No parturient was excluded after randomization. Medication was prepared by an assistant not involved in the study. When the medications were prepared, the assistant gave them to anesthesiology resident who was not involved into the study and was responsible for performing spinal anesthesia. Before performance of spinal anesthesia, parturients were monitored and received intravenous warmed (37°C) lactated Ringer's solution 15 mL kg^{-1} . Oxygen 5 L min^{-1} was administered through a Hudson mask during anesthesia and parturient were covered with blankets but not actively warmed. All prepared solutions were warmed to 37°C . Parturients were randomly assigned to receive hyperbaric bupivacaine (0.5%; 10 mg) and meperidine (Actavis, Zug, Switzerland) in a dosage of 10 mg (35 patients; BM group) or matched hyperbaric bupivacaine dosage with equivalent volume of sterile saline (35 patients; B group). By using a midline approach within a 25-gauge Whitacre needle, spinal anesthesia was performed in the sitting position at the inter space of L3-L4. After spinal injection, patients were placed supine with a left lateral tilt.

Study design and assays: The time at the end of injection was determined as T0. By using pinprick, sensory block was evaluated at 1 min intervals for ten min, 5 min intervals for 35 min, then at 10 min intervals until regression to L3. The level of segment blocked during operation and in the Post-anesthesia Care Unit (PACU) was assessed. Shivering intensity was graded with a scale which is described by Crossley and Mahajan (Crossley and Mahajan, 1994). The incidence and intensity of shivering were measured before operation and every 5 min during intraoperative and postoperative period (whole time of the study period). The blood pressure, heart rate, diastolic and systolic blood pressure, core and peripheral temperature, peripheral oxygen saturation and intrathecal opioid-related side-effects were recorded simultaneously with sensory levels and shivering intensity by a blinded observer. Shivering was stopped with IV clonidine ($0.5\text{ }\mu\text{g kg}^{-1}$) after evaluation and grading of shivering intensity in groups for unwanted complication on fetus and mother. Arterial hypotension was defined as a decrease in systolic blood pressure $<80\text{ mm Hg}$ or less than 30% of the baseline value. It was treated with 5-10 mg of ephedrine IV. Metoclopramide 10 mg IV and diphenhydramine 25 mg IV were used for treating nausea and pruritus, respectively. Core and skin temperature were measured by tympanic probes and skin thermometers in axillaries region, respectively, every 15 min during operation and in the PACU. The

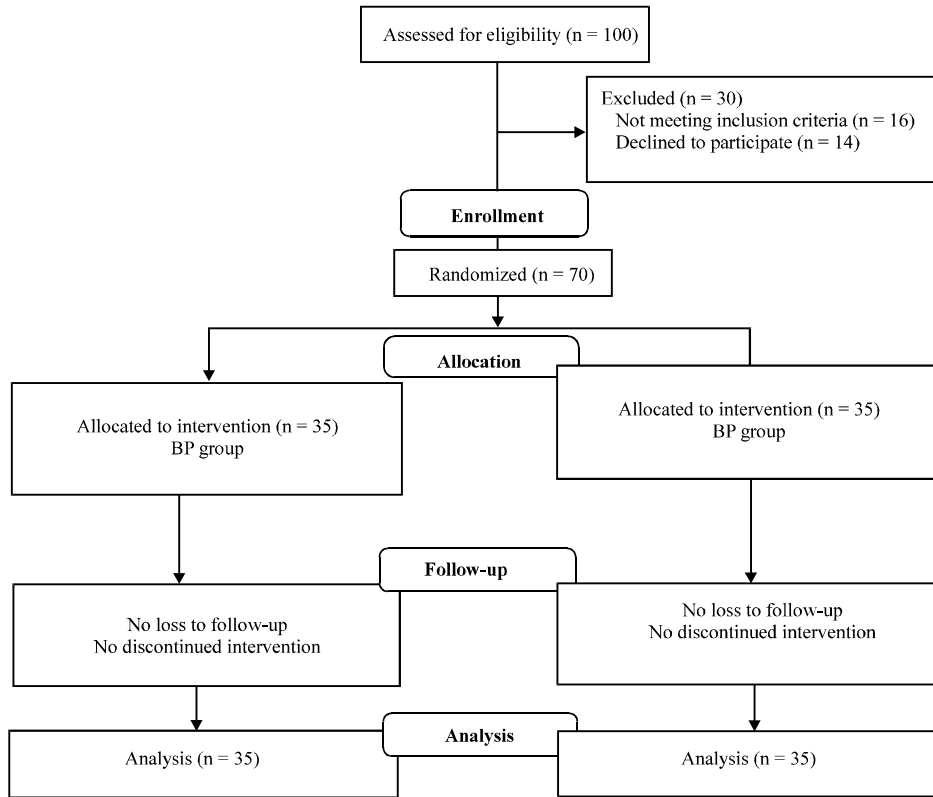


Fig. 1: Participation flow diagram through requirement

temperature of operating room was maintained at 21-23°C. If nausea, vomiting and pruritus had occurred during operation and in the PACU, they were noted. Apgar scores at 1 and 5 min were reported. Surgery duration was also recorded. All data was collected by a blinded observer. Ethical approval for this study (References number: D/A/3755) was provided by the Ethical Committee of Jahrom University of Medical Sciences, Jahrom, Iran (Chairperson M. Poorahmad; M.D.) on 30 July 2012. This trial was registered at www.irct.ir (Trial Number: IRCT2012090410743N1) and <http://www.who.int/ictrp/en/>.

Statistical analysis: Based on the preliminary study, a power analysis was done to find a sufficient sample size in determining a significant difference in intensity and incidence of shivering by using an alpha value of 0.05 and a power of 80%. The incidence of shivering was 65% in group B (P1) and 25% in group BP (P2) in this preliminary study. This established that a sample size of twenty four patients was adequate per group. Thirty five parturients enrolled in each group to compensate for possible none valuable data. The Statistical Package for Social Science (SPSS) for Windows, version 16 (SPSS Inc., Chicago, IL)

was used for data analysis. The quantitative variables (age, weight, height, Body Mass Index (BMI), Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Apgar score, Core and skin temperature, Surgery duration and time to reach highest block, incidence of shivering between groups analysed by Independent t-tests. The highest segment blocked, shivering intensity and incidence and other proportions between groups Compared by chi-square test. Mann-Whitney U-test was used between two-group comparisons by Bonferroni correction if needed. X2 tests or Fisher's exact test as appropriate were used to compare dichotomous nominal variables such as vomiting, nausea, respiratory distress and pruritus. Data are reported as means-standard deviation for 95% confidence interval. A 2-sided p value<0.05 was considered statistically significant.

RESULTS

There were no significant differences between the 2 groups regarding demographic and surgical data, except the time to reach the highest sensory level block, shorter in the group receiving meperidine (Table 1).

Table 1: Demographic and surgery data during the whole time of the study period. Values are Mean±SD or median (range)

Variable	B ^a (n = 35)	BM ^a (n = 35)	p-value
Age (years)	27.12±4.25	28.52±7.30	0.33
BMI (kg cm ⁻²) ^b	23.30±1.70	22.43±2.10	0.06
Basic heart rate (beats per min)	100.92±14.86	105.79±14.75	0.17
Basic SBP ^b (mmHg)	121.76±11.46	120.69±14.56	0.73
Basic DBP ^b (mmHg)	80.53±7.18	80.66±9.50	0.95
Basic peripheral oxygen saturation	99.13±0.83	99.21±0.80	0.68
Basic core temperature	37.05±0.32	37.11±0.26	0.39
Lowest core temperature	36.57±0.40	36.72±0.60	0.22
Lowest peripheral temperature	31.92±0.51	32.18±0.93	0.15
Surgery Duration (min)	57.4±6.5	56.6±9.2	0.67
Time to reach highest block (min)	13.15±3.72	10.31±6.34	0.02
Sensory Level; median (range)	T5 [T2 to T6]	T4 [T3 to T6]	
Apgar			
1 min	8.76±0.19	8.61±0.62	0.17
5 min	9.74±0.12	9.62±0.40	0.09

^aB: Control group. BM: Case group, ^bBMI: Body mass index. SBP: Systemic blood pressure. DBP: Diastolic blood pressure

Table 2: Frequency of adverse effects due to use of meperidine and placebo in the two study groups during the whole time of the study period

Variable	B ^a (%)	BM ^a (%)	p-value
Nausea ^b	0	5(14.2)	0.05
Vomiting ^b	0	3(8.57%)	0.23
Hypotension ^b	16(45.71%)	14(40%)	0.80
Bradycardia ^b	0	1(2.85%)	0.99
Tachycardia ^b	0	0	0.99
Pruritus ^b	0	0	0.99
Administered ephedrine ^b	16(45.71%)	13(37.14%)	0.62
Administered atropine ^b	0	1(2.85%)	0.99
Administered metoclopramide ^b	0	4(11.42%)	0.11

^aB: Control group. BM: Case group, ^bFrequency (percentage) is reported

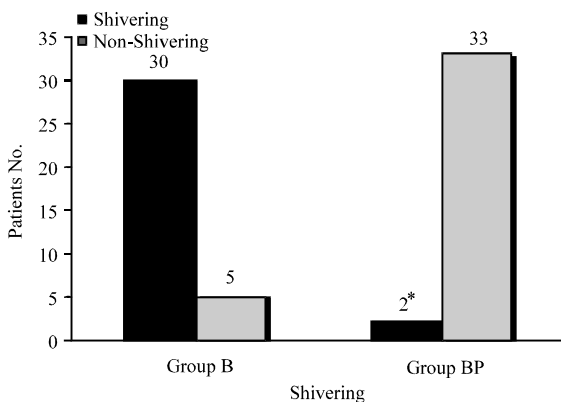


Fig. 2: Incidence of shivering during the whole time of the study period in the meperidine group was significantly lower than the controls: *p<0.05

There were no differences in adverse effects between the two study groups (Table 2).

The incidence of shivering during the whole time of the study period was significantly decreased in the group of parturients who received intrathecal meperidine (p<0.001) (Fig. 2). Shivering was less intense in the BM group compare to B group during the whole time of the study period (p<0.05) (Fig. 3). None of the parturients receiving meperidine experienced grade 3 or 4 shivering, whereas it concerns 8 (22.86%) parturients in the group

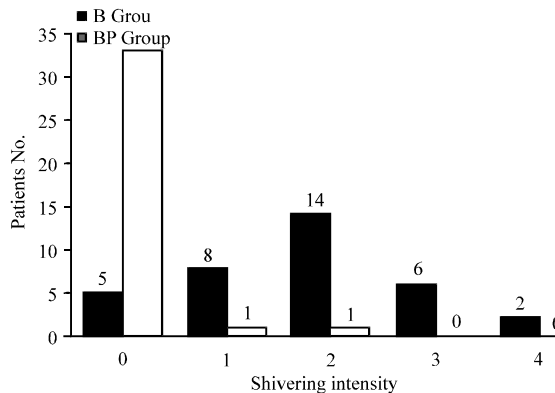


Fig. 3: Shivering intensity for each patient, (0): No shivering, (1): Pillow erection or peripheral vasoconstriction but no visible shivering, (2): Muscular activity in only one muscle group, (3): Muscular activity in more than one muscle group but not generalized shivering; (4): Shivering involving the whole body. Shivering was less intense in the BM group (p<0.05). B group = Control group; BM group = Case group

B (Table 3). Clonidine was used as a rescue for shivering treatment over 2 parturients of BM group and thirty of controls. Need for analgesic drugs was more in the controls (p<0.001). Apgar scores were similar for the two study groups (p>0.05). No patient had to be excluded due to the need for supplementary sedation or inadequate spinal anesthesia.

DISCUSSION

According to reported data, adding small dose of intrathecal meperidine (10 mg) reduces the incidence and intensity of intra- and post-operative shivering of obstetric population in caesarean section under spinal anesthesia without increasing adverse events.

Table 3: Incidence and intensity of shivering in B and BP groups

Group	Non-shivering	Shivering			
		Grade 1	Grade 2	Grade 3	Grade 4
B	14.28% (5/35)	22.86% (8/35)	40% (14/35)	17.15% (6/35)	5.71% (2/35)
BP	94.3% (33/35)	2.85% (1/35)	2.85% (1/35)	0% (0/35)	0% (0/35)
p-value	<0.0001	0.02	0.35	0.02	0.49

B: Control group. BM: Case group, Frequency (percentage) is reported. χ^2 test or Fisher's exact test was used

In the present study, shivering was significantly less intense in experimental group compare to controls. The Authors study are in agreement with the recent studies that showed less intensity of shivering in meperidine used group (Khan *et al.*, 2011; Chen *et al.*, 1993; Roy *et al.*, 2004; Hong and Lee, 2005). In the recent literature, a complete discussion of antishivering mechanism of meperidine can be found (Fukuda, 2005). Meperidine is a synthetic opioid binds to both mu and kappa receptors which are useful for treating moderate to severe pains. Anti shivering effect is due to binding to both alpha and beta-two receptors (Locks, 2012; Bryant *et al.*, 2011). In a Meta-analysis study demonstrated that just 1.3 patients need to be treated stop shivering in one single patient after administration of IV meperidine. (Kranke *et al.*, 2004) Prevention of shivering has not been fully understood, as compared with treatment. The alfentanil, morphine and fentanyl are not as effective as meperidine in treating shivering (Pang *et al.*, 1998; Nishikawa *et al.*, 2000; Karakaya *et al.*, 2001). In present study, the author used intrathecal form of meperidine for its antishivering effect. Recent data showed that intrathecal meperidine is more useful than IV and IM forms of meperidine in reducing severity and incidence of shivering (Hu *et al.*, 1992; Nordberg *et al.*, 1988) it may because of types of receptors that they may involve. The authors study data suggested the preliminary findings.

This dose of meperidine doesn't have specific side effects. In the present study, there is not any significant incidence of postoperative side effects including nausea, vomiting and respiratory distress. In contrast, other studies reported nausea and vomiting as side-effects of meperidine during spinal anesthesia for caesarean section. Meperidine is metabolized to norpethidine which has CNS toxic effects. Doses of 25 mg are associated with supratoxic levels of norpethidine (Nordberg *et al.*, 1988). High dosage of meperidine is along with side effects such as vomiting, nausea, drowsiness, bronchospasm, respiratory depression, pruritus, hypotension, bradycardia and central nervous system excitatory (Freye, 1974; Morisy and Platt, 1986; Kaiko *et al.*, 1983). In the recent study, the use of intrathecal meperidine (12.5 or 25 mg and 0.2 mg kg⁻¹) for caesarean section during spinal anesthesia for the prevention of shivering was not recommended as its use is associated with

increased incidence of nausea and vomiting (Khan *et al.*, 2011; Chen *et al.*, 1993; Roy *et al.*, 2004). Nausea and vomiting are troublesome side effects which are encountered during spinal anesthesia for caesarean section. On the basis of these findings, single-shot, mini-dose intrathecal meperidine is not associated with side effects. It seems that meperidine induced nausea and vomiting was decreased may due to low sympatholysis effect of single-shot intrathecal meperidine, relatively. In the study of English literature, Roy *et al.* (2004), showed that using low dose (0.2 mg kg⁻¹) intrathecal meperidine reduces the incidence and intensity of shivering but side effects related to meperidine, such as vomiting and nausea were not noted in their study (Roy *et al.*, 2004). As, these finding are in controversy with previous studies, the idea seems intriguing and could be pursued in future studies in different literatures.

As same as with the previous studies (Khan *et al.*, 2011; Hong and Lee, 2005), in this study, data showed no significant differences in core and peripheral temperatures between groups. The effect of meperidine on core temperature is species-dependent and complex. In animal models large doses of meperidine can cause hypothermia. Moreover, the hypothermic effect is intensified by the low environmental temperatures. The role of warming fluids in decreasing hypothermia has been attributed to in other studies (Hong and Lee, 2005). Although, parturient have not been actively warmed in this study but the fluids infusion were warmed. As it is shown in Table 1, parturient were failed to prevent parurient from becoming hypothermic.

The present study finding showed the time to maximal block was significantly shorter in the experimental group: This effect was directly commensurate to low level of meperidine dose. These results offered that meperidine added to hyperbaric bupivacaine does not prolong total anesthesia time. Furthermore, sensory block was at the desired level of T4 in both groups and with regard to level of sensorial block, no significant differences between groups were observed. The same level of sensorial block in both groups indicated that firstly, the development of hypothermic is related to the equal potential effects of block height and secondly, sensory block height was not influenced by intrathecal meperidine. These data were similar to the results found by Roy *et al.* (2004).

In the present study the mean Apgar score of the newborns in 1 and 5 min were 8 and 9, respectively and no significant differences were observed among experimental group. The studies of intrathecal meperidine effects on neonates and fetus of mothers who were under spinal anesthesia for caesarean section demonstrated no significant side effects (The umbilical cord blood base/acid status, blood gas and Apgar scores of such infants were measured) (Nordberg *et al.*, 1988; Freye, 1974; Morisy and Platt, 1986).

The present study had some advantages and limitations. The advantage of this study is that authors do not dichotomize continuous variables data which gives an additional impact on exactness. The authors acknowledge that the only one dose was studied and this doesn't allow drawing any definitive conclusions. Therefore, a dose-effects study is required for confirming the data.

The authors concluded that using single-shot, mini-dose intrathecal meperidine (10 mg) reduces the severity and intensity of intra- and post-operative shivering in caesarean section under spinal anesthesia without increasing adverse events. Other studies should be designed and compare with the present study. It is suggested that small dose of intrathecal meperidine should be used to prevent shivering in parturients scheduled for elective caesarean section under spinal anaesthesia.

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