RESEARCH ARTICLE

Evaluating the Effect of Intrathecal Sufentanil and Meperidine on Shivering after Caesarean Section under Spinal Anesthesia

Anahita Hirmanpour[1], Reihanak Talakoub[1], Amir Shafa[1]*, Navid Chitsaz[1]

Background: The present study has evaluated the effect of intrathecal Sufentanil and Meperidine on patients' shivering after caesarean section.

Methods: The present study was a double-blind randomized clinical trial that was conducted on 120 patients. Spinal anesthesia was administered using 2 cc (10 mg) of bupivacaine along with 2.5 µg (0.5 cc) of Sufentanil for the first group, 25 mg (0.5 cc) of Meperidine for the second group and 0.5 cc normal saline for the control group.

The severity of patients' shivering was recorded during the surgery and in the recovery room. Heart rate, respiratory rate, systolic and diastolic blood pressures, oxygen saturation, and core and skin temperatures were measured before anesthesia, 5th minute, 10th minute and then every 15 minutes until the end of the surgery and then every 15 minutes into the recovery until discharge from recovery. The Apgar score of the neonates were also recorded at the 1st and 5th minutes after birth.

Results: The mean score of shivering was significantly lower in the Meperidine group (0.1 ± 0.07) than the Sufentanil group (1.2 ± 0.3) and the control group (4.1 ± 0.5) ($p< 0.05$). The frequency of incidence of shivering was also decreased in Meperidine (5.3%) and Sufentanil (42.1%) groups compared to the control group ($p< 0.001$). Changes in blood pressure from the 25th minute to the 45th minute of the surgery and during the first 45 minutes into the recovery had more stability in the Meperidine and Sufentanil groups ($p< 0.05$). Changes in the heart rate respiratory rate, core and skin temperatures and infants' Apgar score had no statistical difference between the three groups ($p > 0.05$).

Conclusion: Using intrathecal Meperidine and Sufentanil, besides decreasing the incidence of shivering (with more effectiveness from Meperidine), would also increase the block density and quality of relaxation in the patients. It would also lead to improved hemodynamic stability without affecting the sensory block level and infant's Apgar score.

Keywords: sufentanil; meperidine; caesarean section; shivering

Caesarean section is a surgery which is conducted by making a surgical cut on the abdominal wall and the uterus of pregnant women for delivering the babies. Caesarean section is the most performed surgery for women and has increased significantly during the recent years [1].

Spinal anesthesia is the preferred method for elective and urgent caesarean sections [2-3]. Due to its quickness, simplicity and reliability in causing sensory and motor inhibition, this method has increasingly become the selected method for caesarean section [4].

Opioids that would be added to local anesthetics may decrease the required dose for each drug; furthermore this drug could decrease the hemodynamic effects in the patient [5-6]. The scientific basis for adding opioids to intrathecal topical anesthetics is that these opioids would act synergistically with the local anesthetic [4].

Meperidine is a moderate lipophilic opioid and has a significant local anesthetic effect [7]. Traditionally, this opioid was the only factor used for spinal anesthesia in caesarean section [8].

Sufentanil is a lipophilic opioid that would improve analgesia during and after the surgery for the mother and the infant with no side effects [4,9].

Shivering after surgery is a common complication at the post-anesthesia care unit or recovery room and its prevalence in general anesthesia is 5-65% and in neuraxial anesthesia is 33% [10].

Shivering is a protective reflex that would increase body temperature through muscle contraction [11]. Shivering is a common complication following spinal anesthesia that may lead to serious problems such as increased oxygen consumption, carbon dioxide production, pulmonary ventilation, heart's workload and also decreased venous oxygen saturation [12]. Mother's shivering may cause distress and harmful side effects for her [13]. On the other hand, hypothermia may lead to inhibition of platelet function, inhibition of coagulation factors and even

From the [1]Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.

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*Corresponding author: Amir Shafa, MD, Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: shafa_amir@yahoo.com

inhibition of drugs' metabolism which consequently may cause post-surgical complications like postoperative bleeding, prolonged effect of relaxants, delay in patient's awakening and eventually longer stay at the recovery room [14].

Different theories have been discussed as the mechanism of shivering. One of these theories has demonstrated that brain and spinal cord do not come out of anesthesia at the same time and the hypothermia caused may lead to shivering. Another recommended mechanism suggested the function of kappa opioid receptor, N-methyl-aspartate receptor and 5-hydroxytryptamine [15].

Different studies have evaluated the effect of intrathecal meperidine [15-19] and sufentanil [15-20] and also their effect on shivering after caesarean section and other surgeries. But, so far, no studies have compared the effect of these two drugs on reduction of shivering in patients after caesarean section with spinal anesthesia and no valid evidences exist for selecting one of these two drugs. The present study was conducted to compare the effect of intrathecal prescription of these two drugs on shivering following caesarean section with spinal anesthesia.

Methods

The present study was a double-blind randomized controlled clinical trial that was conducted at Shahid Beheshti and Al-Zahra hospitals of Isfahan during 2015-2016 after taking written informed consent from the patients.

Study population was pregnant women, ASA I/II status, scheduled for elective caesarean section with spinal anesthesia who were divided into three groups by random allocation.

The inclusion criteria were having a normal pregnancy with no complications, having no contraindication for local anesthesia and being taller than 150 cm. Patients with systemic diseases (preeclampsia, liver and renal diseases (hepatorenal) and bleeding causing problems), diagnosed fetal anomaly, placenta previa, placental abruption and allergy to any of the studied drugs were not enrolled in the study.

The exclusion criteria were any changes in the anesthesia method, any condition that lingers the surgery for more than two hours, patient's need for blood transfusion and patient's atony and need for using misoprostol.

120 patients were enrolled in the study and randomly allocated into three groups of 40 participants: intratechal Meperidine, Sufentanil and control (placebo). Two participants from the control group and one from each of the other groups were excluded from the study due to changing the surgical method to general anesthesia.

After hydration with 10cc/kg of normal saline for 20 minutes before the spinal anesthesia, patients were put under electrocardiogram, non-invasive blood pressure and pulse oximetry monitoring. Spinal anesthesia was performed in sitting condition at the L3L4 or L4L5 lumbar level after prepping, using a size 25 needle of Quincke model after the flow of CSF with 2 cc (10 mg) of 0.5% bupivacaine along with the studied drugs for each of the three groups. The first group received 2.5 mg (0.5 cc) of Sufentanil, the second groups received 25 mg (0.5 cc) of Meperidine and the third group received 0.5 cc normal saline and then, immediately, all the patients were laid down supinely with a wedge beneath their right hip. Patients received oxygen through a face mask with the flow of 3 liter. In case of a drop in the average blood pressure more than 10% of the baseline, 10 mg of ephedrine was administered. This dose was repeated if needed. The nurse anesthetist prepared the studied drug for each group and the anesthesiologist who performed the spinal anesthesia had no information about the type of the drugs.

Heart rate, respiratory rate, systolic, diastolic and mean blood pressures, arterial oxygen saturation and core temperature (using a tympanometer of Omron model) and surface temperature (using a thermometer of Omron model) were measured and recorded before the start of the spinal anesthesia, at the 5th and 10th minutes of the surgery and then every 15 minutes into the surgery, after entering the recovery room and then every 15 minutes until being discharged from the recovery room. After the surgery patients were wrapped with a blanket and none of them were warmed up actively. The temperature of the operating room for each patient was also recorded.

The maximum block sensory level was checked and recorded using pin prick method 15 minutes after the start of the spinal anesthesia.

Patients' level of drowsiness during the surgery was measured in four scales:

1- Awake and anxious, 2- Awake and calm, 3- Asleep but easily awaken and 4- Asleep but not easily awaken

The severity of patients' shivering was also measured and recorded in four grades from the beginning of the surgery:

1- No shivering, 2- Brief fasciculation in one muscle group, 3- Muscular tremor in two muscle groups and 4- Tremor in the entire body (more than two organs)

In case of a shivering of grade 3 or higher, the patient received 25 mg of intravenous meperidine. The Apgar scores of the infants were also recorded 1 and 5 minutes after the delivery.

In case of nausea and vomiting, patients received 4 mg of intravenous ondansetron. Patients with itching received 20 mg of propofol and if not resolved, received 0.1mg to 0.4mg of naloxone.

The surgeon's satisfaction with muscle relaxation was evaluated as poor (1), medium (2) and good (3).

Patients were released from the recovery room after diminished neuroaxial block (bromage scale no: 1) [the Bromage scale (0, no block; 1, impaired hip flexion; 2, impaired hip and knee movement; and 3, impaired hip, knee and ankle movement)] and the absence of nausea and vomiting and hemodynamic stabilization. After regression of sensory level in the place of incision using vas scale from 0 to 10, patient's pain was measured and recorded. If the VAS scale was 3 or higher, a 10 mg diclofenac suppository was prescribed.

Data were analyzed using SPSS 20 (SPSS Inc., Chicago, IL, USA) and Chi-square, Kruskal-Wallis and one-way ANOVA tests.

Results

The present study was conducted to evaluate the effect of Sufentanil and intrathecal Meperidine on shivering after caesarean section with spinal anesthesia in Shahid Beheshti hospital of Isfahan during 2015-2016 and the results compared with the control group.

Regarding the quantitative data, one-way variance analysis showed no significant difference between the three groups.

(Table 1).

One-way variance analysis showed a significant difference between the severity of shivering's scores of the three groups ($p<0.001$); in a way that the mean score of the Meperidine group was lower than the Sufentanil group and the score of the Sufentanil group was lower than the control group. Furthermore, the prevalence of shivering in the Sufentanil group and the Meperidine group was, respectively, 42.1% and 5.3% less than the control group (81.2%) (Table 2).

Table 1- Means of various numerical variables in three groups

Variables	Meperidine	Sufentanil	Control	P-value
Age (year)	30.9 ± 5.9	31.1 ± 5.6	31.1 ± 4.9	0.98
BMI	29.9 ± 3.8	30.4 ± 5.2	30.6 ± 4.6	0.83
Number of pregnancy	2.2 ± 0.8	2.02 ± 0.9	2.1 ± 0.7	0.60
GA (week)	38.2 ± 0.8	38.3 ± 0.7	38.1 ± 0.9	0.74
room temperature	24.4 ± 0.6	24.6 ± 0.5	24.3 ± 0.6	0.13
PACU stay time (min)	65.1 ± 13.6	70.7 ± 16.2	64.7 ± 20.7	0.25

Datas are presented as mean ± SD
There were no statistically significant between-group differences ($P > 0.05$).

Table 2- Frequency and mean of shivering in three groups

Variable	Meperidine group	Sufentanil group	Control group	P-value
Intensity of shivering (Mean ± SD)	0.1 ± 0.07	1.2 ± 0.3	4.1 ± 0.5	<0.001
Frequency of shivering n(%)	2 (5.3)	16 (42.1)	26 (81.2)	<0.001

$P<0.05$ is statistically significant.

The mean of systolic blood pressure at the 25th, 40th and 55th minutes of the surgery and the 15th and 30th minutes of the recovery had a significant difference between the three groups but no significant difference was observed between the three groups at the other times ($p > 0.05$).

The mean of diastolic blood pressure at the 15th and 45th minutes of the recovery had a significant difference between the three groups but the difference was not significant at the other times ($p > 0.05$) (Figure 1-2).

Times in all figures are expressed as:

1. Before starting the spinal
2. 5 minutes during surgery
3. 10 minutes during surgery
4. 25 minutes during surgery
5. 40 minutes during surgery
6. 55 minutes during surgery
7. Arrival to recovery
8. 15 minutes after arrival to recovery
9. 30 minutes after arrival to recovery
10. 45 minutes after arrival to recovery
11. 60 minutes after arrival to recovery

Figure 1- Mean of systolic blood pressure in three groups in different times

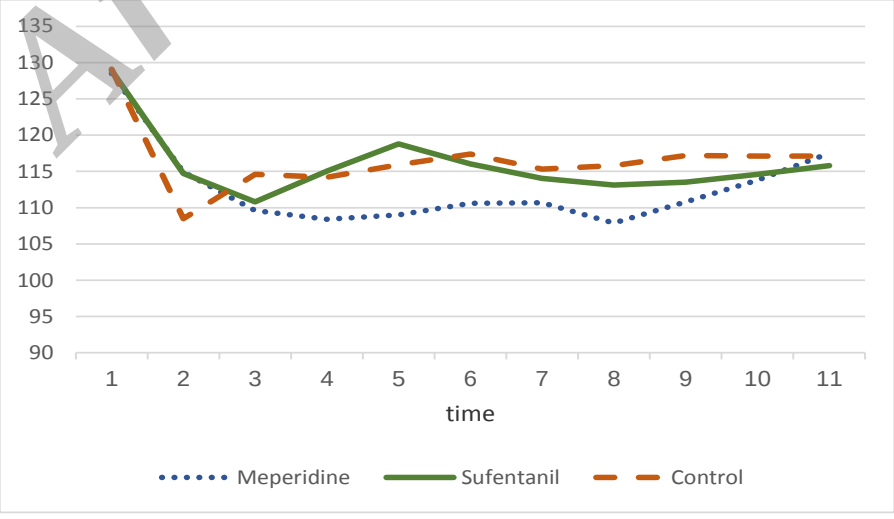
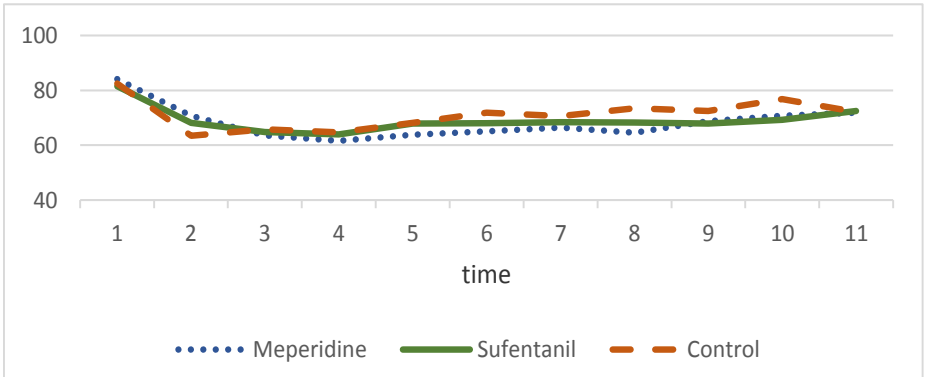


Figure 2- Mean of diastolic blood pressure in three groups in different times



The mean of average arterial blood pressure at the 15th and 45th minutes of the recovery was significantly higher in the control group compared to the other two groups but no significant difference was observed between the groups at the other times ($p > 0.05$). (Figure 3)

The mean of heart rate had no significant difference between the three groups at any of the measured times ($p > 0.05$). (Figure 4)

Figure 3- Mean of MAP in three groups in different times

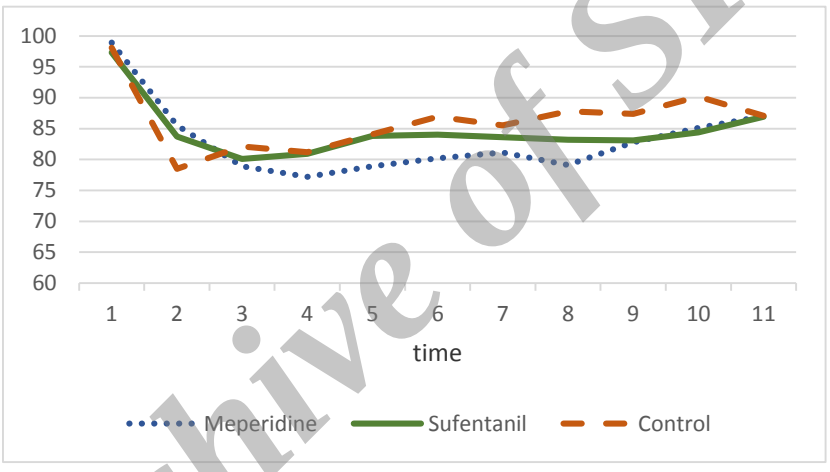
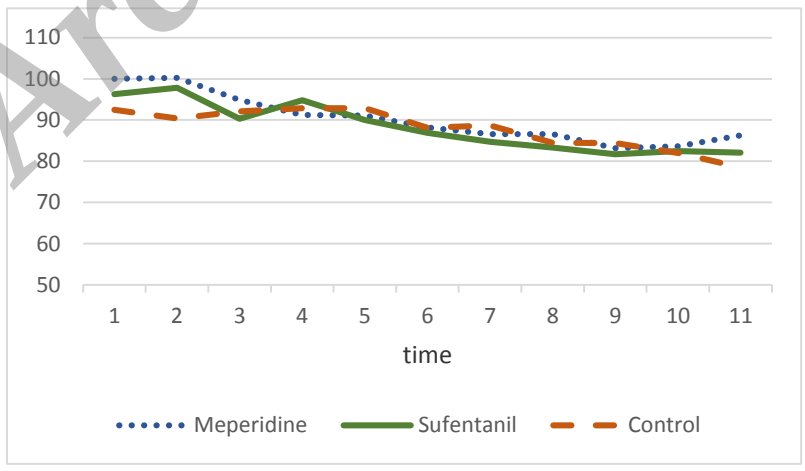


Figure 4- Mean of heart rate in three groups in different times



Regarding the mean of SpO2, no significant difference was observed between the groups at any of the measured times ($p > 0.05$). The mean of respiratory rate at the 25th, 40th and 55th minutes of the surgery and the 30th minute of the recovery was significantly higher in the control group compared to the other two groups and was higher in the Sufentanil group than the Meperidine group. The difference at the other measured times was not significant ($p > 0.05$). (Table 3)

Table 3- Means of SpO_2 and respiratory rate at different times in three groups

Variable	time	Meperidine Mean ± SD	Sufentanil Mean ± SD	Control Mean ± SD	P-value
	1	97.9 ± 1.1	97.7 ± 1.4	97.6 ± 1.2	0.79
	2	97.8 ± 1.8	98.1 ± 1.3	97.5 ± 1.2	0.32
	3	97.8 ± 1.5	97.9 ± 1.2	98.2 ± 1.2	0.56
	4	97.8 ± 1.6	97.7 ± 1.5	97.5 ± 1.5	0.60
	5	97.5 ± 1.9	97.7 ± 1.8	97.6 ± 1.4	0.84
SPO2	6	97.8 ± 1.7	97.8 ± 1.5	98.4 ± 1.4	0.34
	7	98 ± 1.4	97.6 ± 2.01	98.1 ± 1.1	0.40
	8	97.4 ± 1.8	97.5 ± 1.9	97.4 ± 1.8	0.84
	9	97.9 ± 1.3	97.5 ± 1.7	97.6 ± 1.01	0.56
	10	97.8 ± 1.5	97.9 ± 1.4	97.6 ± 1.7	0.99
	11	97.9 ± 1.2	97.7 ± 1.3	97.8 ± 1.1	0.84
	1	14.7 ± 3.4	13.5 ± 2.1	13.6 ± 2.3	0.12
	2	14.1 ± 3.3	13.6 ± 2.6	14.2 ± 4.02	0.75
	3	14.02 ± 3.5	13.7 ± 3.2	15.5 ± 3.9	0.16
	4	13.9 ± 3.4	14.2 ± 2.9	15.9 ± 3.9	0.04
	5	13.6 ± 2.4	14.2 ± 2.5	15.6 ± 4.3	0.008
RR	6	13.7 ± 2.7	13.9 ± 2.4	15.4 ± 3.3	0.03
	7	13.5 ± 2.4	13.8 ± 2.1	14.3 ± 2.9	0.61
	8	13 ± 2.5	13.6 ± 2.2	14.7 ± 2.7	0.27
	9	14 ± 2.4	13.6 ± 2.2	14.7 ± 2.7	0.02
	10	14.7 ± 2.5	13.5 ± 1.8	14.8 ± 2.8	0.09
	11	13.5 ± 2.6	13.6 ± 2.1	14.8 ± 2.3	0.07

P<0.05 is statistically significant.

Times description:

1. Before starting the spinal
2. 5 minutes during surgery
3. 10 minutes during surgery
4. 25 minutes during surgery
5. 40 minutes during surgery
6. 55 minutes during surgery
7. Arrival to recovery
8. 15 minutes after arrival to recovery
9. 30 minutes after arrival to recovery
10. 45 minutes after arrival to recovery
11. 60 minutes after arrival to recovery

One-way variance analysis showed no significant difference between three groups regarding their mean of core and surface temperatures at any of the measured times (p> 0.05). (Figure 5-6)

Figure 5- Mean of central temperature in three groups in different times

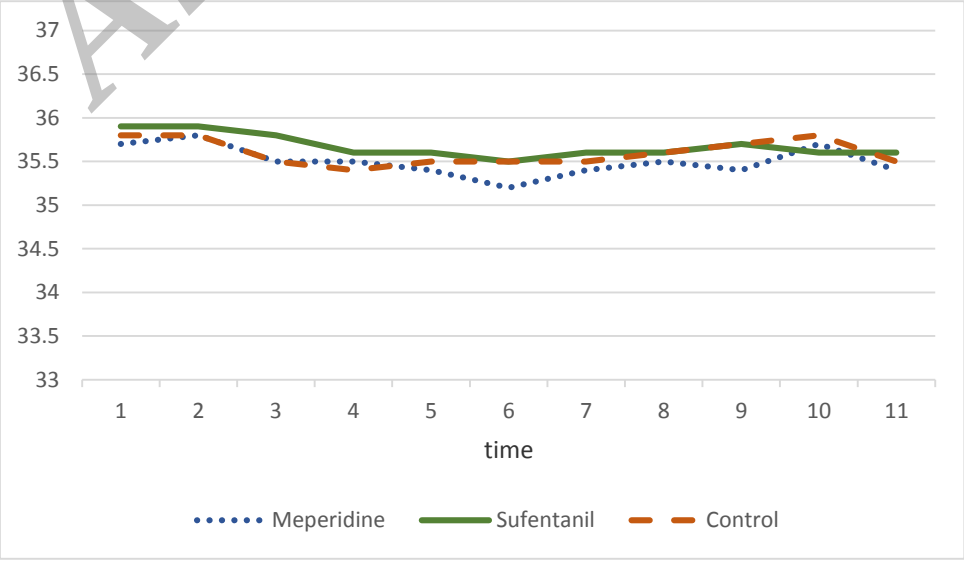
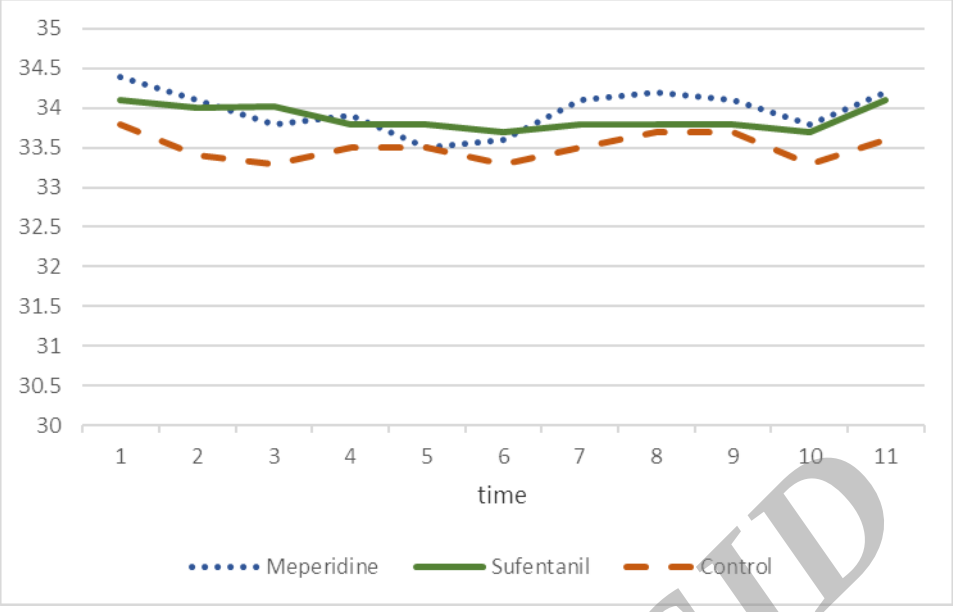


Figure 6- Mean of peripheral temperature in three groups in different times



One-way variance analysis revealed that the difference between the Pethidine (p< 0.001) and the ondansetron (p= 0.01) of the three groups was statistically significant (Table 4).

According to one-way variance analysis, no significant difference was observed between the mean of Apgar score of the infants in the three groups at the 1st (p= 0.68) and 5th (p= 0.80) minutes (Table 5).

Kruskal-Wallis test revealed that the level of surgeon's satisfaction with muscle relaxation had a significant difference between the three groups (p< 0.001); in a way that surgeon's satisfaction in the Sufentanil group was higher than the control group and in the Meperidine group was higher than the Sufentanil group (Table 6).

Chi-square test showed that the prevalence of vomiting (p= 0.02) and dropped blood pressure (p= 0.008) was significantly lower than the two other groups but the prevalence of itching in the Sufentanil group was higher than the Meperidine group and in the Meperidine group was higher than the control group (p< 0.001) (Table 6).

Table 4- Mean of received pethidine and ondansetron in three groups

Variable	Meperidine Mean ± SD	Sufentanil Mean ± SD	Control Mean ± SD	P-value
Pethidine	0	7.2 ± 2.3	35.2 ± 5.2	<0.001
Ondansetron	3.6 ± 0.4	1.8 ± 0.4	2.6 ± 0.3	0.01

Table 5- Mean of Apgar score at 1 and 5 minutes in three groups

Apgar score	Meperidine Mean ± SD	Sufentanil Mean ± SD	Control Mean ± SD	P-value
Minute 1	8.9 ± 0.2	8.9 ± 0.3	9± 0.2	0.68
Minute 5	10 ± 0.1	9.9 ± 0.2	10 ± 0.1	0.80

Table 6- Frequency of Maximum level of sensory block, Surgeon satisfaction level and Complications in three groups

Variable	Meperidine N (%)	Sufentanil N (%)	Control N (%)	P-value
Maximum level of sensory block				
T3	2 (5.3)	0	1 (3.1)	
T4	15 (39.5)	13 (34.2)	9 (28.1)	
T5	10 (26.3)	17 (44.8)	11 (34.4)	
T6	11 (28.9)	6 (15.8)	9 (28.1)	0.52
T7	0	1 (2.6)	0	
T8	0	1 (2.6)	2 (6.3)	
Surgeon satisfaction level				
excellent	28 (100)	29 (87.9)	13 (46.4)	
moderate	0	4 (12.1)	15 (53.6)	<0.001
bad	0	0	0	
Complications				
vomiting	26 (68.4)	15 (39.5)	21 (65.6)	0.02
low blood pressure	11 (28.9)	1 (2.6)	7 (21.9)	0.008
pruritus	14 (36.8)	24 (63.2)	1 (3.1)	<0.001

P<0.05 is statistically significant.

Discussion

The most important finding of the present study was the 39.1% decrease in the shivering after prescription of intrathecal Sufentanil [16] which is in line with the results of previous studies and also the 75.9% decrease in shivering in the Meperidine group compared to the control group.

Since spinal anesthesia with high sensory block level is one of the risk factors for hypothermia and occurrence of shivering in the patients, using intrathecal Sufentanil and Meperidine could decrease the prevalence of shivering and its related complications and also make no difference in patients' level of sensory block [17-18].

A study that was conducted in 2010 mentioned that combined administration of bupivacaine and Meperidine, in comparison to administration of bupivacaine alone, may decrease the prevalence of side effects with no negative effect on the quality of anesthesia or patient's and surgeon's satisfaction [19]. Even the anti-shivering effect of Meperidine along with intrathecal Lidocaine has been proven in prostate surgeries [18].

Vasodilatation that occurs below the block level would lead to redistribution of body temperature from the central compartment to the peripheral compartment. This matter, as the normal mechanism of shivering, would decrease the core body temperature that was obviously observed in the present study [20].

Another important finding of the present study was surgeon's high level of satisfaction with muscle relaxation during the surgery in the groups that received intrathecal drugs; so these two drugs may be used for improving the quality of blockage in spinal anesthesia.

Also, in the present study, respiratory rate was lower during the surgery in the groups that received intrathecal drugs but no apnea or respiratory complications were observed in the patients that could be explained by the property of intrathecal drugs and also the findings of previous studies [21].

Another previously conducted study resulted that adding a low dose of Meperidine to Lidocaine for the spinal anesthesia of caesarean section may be effective, and also safe, for decreasing the prevalence and severity of shivering in patients [22].

Barga et al revealed that adding Sufentanil to bupivacaine would provide an appropriate anesthesia for caesarean section and painlessness after the surgery and may decrease delayed anesthesia, increase the duration of numbness, increase the quality of anesthesia, and cause no fetal complications [23]. However, in the present study, painlessness after surgery was not assessed.

Also adding Sufentanil to intrathecal bupivacaine for spinal anesthesia of caesarean section would increase painlessness after surgery and improve patient's hemodynamic stability, with the least occurred side effects [4]. The present study also showed that injection of intrathecal Sufentanil and Meperidine has led to more hemodynamic stability in patients compared to the control group and patients had a higher average arterial blood pressure during the surgery. This is one of the advantages of using intrathecal Sufentanil and Meperidine especially in pregnant women.

The study of Honarmand et al has proven the effect of intrathecal Meperidine in decreasing the prevalence of shivering and decreasing the consumption of Pethidine to treat shivering and also hemodynamic stability of the patients which is similar to the findings of the present study [24].

In another study, adding Sufentanil to levobupivacaine for caesarean section increased the pace of sensory and nerve block and also increased the duration of analgesia which consequently decreased the need for painkillers [25].

In a study that was conducted in 2012, for spinal anesthesia during caesarean section, one group of women received bupivacaine along with intrathecal morphine and for the other group Sufentanil was also added to the above combination. The second group had a lower prevalence of shivering after surgery than the first group [26]. This result was also found in the present study.

In 2015 Abdollahpour et al showed that adding Sufentanil or midazolam to bupivacaine, compared to the administration of bupivacaine alone, had no effects on infants' Apgar score but decreased the prevalence of shivering in patients after caesarean section with spinal surgery [27].

Another study in 2016 revealed that administration of bupivacaine and Sufentanil, compared to the administration of bupivacaine alone, decreased the pain and shortened the onset of sensory block; however it increased the prevalence of itching [28]. The result of the present study regarding the prevalence of itching is also in line with the results of previous studies and it was significantly higher in the group that had received intrathecal Sufentanil than had the group that received intrathecal Meperidine.

Another important result of the present study which is similar to the results of previous studies [4,5,19-25], was that the intrathecal administration of these two drugs had no effects on the infants' Apgar score; so that they could be used for pregnant mothers with no concern.

Conclusion

The present study showed that administration of intrathecal Sufentanil and Meperidine, not only decreased the prevalence of shivering (with more effectiveness of Meperidine on shivering) and the need for Pethidine to treat shivering, but also Meperidine increased the density of the block and led to a higher quality of patient's relaxation during surgery. Furthermore, it also resulted in better hemodynamic stability of the patients with no effect on the sensory block level and infants' Apgar score.

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