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Original Article

Continuous spinal anesthesia with sufentanil in labor analgesia can induce maternal febrile responses in puerperas

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Abstract: Several studies documented persistent hypothermia in parturients after spinal anesthesia, while others reported that labor analgesia was related to a high incidence of fever. Continuous spinal labor anesthesia with sufentanil (CSLAS) is a new effective technique in labor analgesia but whether it affects maternal temperature has not been clarified. The aim of our study was to explore the relationship between CSLAS and maternal intrapartum temperature during vaginal delivery. Methods: 75 healthy term nulliparas of spontaneous labor were randomized to receive CSLAS during delivery in sufentanil group (n=37) or non-pharmacological methods of pain relief in control group (n=38). The maternal tympanic temperature was recorded at each time points we required during labor. IL-6, IL-8 and TNF-α were sampled at baseline (before analgesia) and 5 minutes after delivery. The data on visual analog scale (VAS) in all puerperas, first and second stage durations of labor, vaginal examination, oxytocin augmentation, maternal and neonatal antibiotic therapy, maternal and neonatal infection, need for cesarean section, need for instrumental delivery and Apgar scores were all collected from the patients' medical records. Result: Baseline characteristics of parturients in the 2 groups were not significant differences. After intrathecal injection of sufentanil, the sensation of pain was attenuated by a wide margin in the sufentanil group compared with the control group. Nine parturients in the sufentanil group (24.32%) and two in the control group (5.26%) had a tympanic temperature above 38°C during the labor (p=0.024). In each group, there was a tendency that maternal temperature elevated gradually with time elapsing and reached the peak value 5 hours after baseline. The changes had significant difference from 3 hours to 7 hours after analgesia compared with baseline. Maternal serum IL-6 and IL-8 levels were increased during the labor, while TNF-α did not vary at any time point in each group. 1 min and 5 min Apgar scores were not significant difference in the two groups and no neonate developed temperature above 38°C in the first 24 hours and with antibiotic therapy. Conclusion: The technique of continuous sufentanil spinal labor anesthesia is a safe and effective method in labor analgesia; however, it is associated with an increased incidence of maternal fever.

Keywords: Analgesia, sufentanil, continuous spinal labor anesthesia, CSLAS, maternal temperature, fever, labor pain

Introduction

Continuous spinal labor anesthesia with sufentanil (CSLAS) into the subarachnoid space via an indwelling catheter is a new reliable technique in labor analgesia, which has benefits to meet the request of analgesia and faster pain relief among puerperas. Both of these advantages bring about the rate of maternal satisfaction higher than normal labor [1]. However, several studies reported that intrapartum fever is associated with epidural or combined spinal-epidural analgesia during labor [2-4]. Sometimes, this adverse event is associated with the increase of extra oxygen consumption in important organs, the unnecessary administration of antibiotics, the redundant catecholamine production and the risk evaluation of

sepsis for neonates [5]. As we known, the mechanism of this fever is still unclear. One theory is that epidural analgesia changes the regulation of temperature [6]. Another one is that epidural analgesia leads to longer labor with multiple interventions, which may increase the risk of chorioamnionitis to generate maternal fever [7, 8].

CSLAS is a method using sufentanil on labor anesthesia, whether it has relationship to intrapartum fever and whether the fever has an effect on neonates; even the pathogenesis of this is still unclear. To our knowledge, the effect of CSLAS on intraparietal temperature has not been previously reported. The aim of our study was to investigate the relationship between CSLAS and maternal intrapartum fever during vaginal delivery.

Materials and methods

This protocol was approved by the Study Institutional Ethics Committee (Obstetrics and Genecology Hospital, Fudan University, Shanghai, China) and written informed consent was obtained. Inclusion criteria are as follows: nulliparity, term pregnancy (>37 weeks), vertex presentation, intent to relieve labor pain by means of CSLAS and be able to provide informed consent for this. Parturients who had a baseline temperature of 37.5°C and above, metabolic disease, contraindications to intraspinal analgesia and pregnancy-related complication such as diabetes mellitus or preeclampsia were excluded. And also, parturients who delivered within 2 hours or over 8 hours after analgesia and needed for cesarean delivery were excluded because the data of different time points we preferred were not available.

The criterion of sample size calculating was as follows: α=0.05, Z_{α}=1.96, power of 80%, Z_{β}=0.84, the incidence of fever was defined as 26.2% [9, 10] in sufentanil group and 1.6% [11] in the control group. At least 60 women would be required to fulfill the criterion and we enrolled 90 to select.

The eligible women were enrolled in this controlled, prospective clinical trial and randomly assigned to 2 groups using a computer random number generator: sufentanil group (women received CSLAS analgesia to relieve labor pain), control group (normal labor with non-pharmacological methods). The baseline characteristics of maternal age, weight, height, cervical dilatation, duration of pregnancy, VAS score, neutrophil and white blood cell count were abstracted before analgesia started.

In sufentanil group, CSLAS was performed using a new macro spinal catheter system for continuous spinal anesthesia (CSA) and labor pain management. The epidural space was identified with an epidural Crawford needle using loss of resistance to air method at L2-3 or L3-4 intervertebral space in either right or left lateral position. The 29-gauge needle covered by a catheter (Spinocath®-B. Braun Melsungen, Germany) was passed through the epidural needle and pierces the dura mater. The catheter-over-needle system was introduced through the Crawford needle until CSF freely flowed within the catheter. The metallic guide was then withdrawn along with the spinal needle and simultaneously, a catheter was inserted 3 cm into the intrathecal space. Finally, the catheter was secured and the woman was placed in the supine position with approximately 15° left tilt. We administered isobaric sufentanil 6 ug, which was diluted by cerebrospinal fluid to 1.5 ml and slowly injected in 5 seconds. After that, the catheter was connected to an electronic pump (Acemedical AM3300, Korea) with a solution of sufentanil being diluted to 2 ug/ml. The continuous infusion rate was 2 ml/h with a 15 minutes lockout interval of 1 ml bolus. In this study, VAS score was recorded successively at the time points of the baseline (before labor analgesia), 5, 10, 15 minutes, 1, 2, 3, 4, 5, 6, 7, 8 hours after labor analgesia to assess the efficiency of CSLAS and ensure the analgesia. Effective analgesia was limited to VAS score <3. If pain relief was inadequate (VAS score ≥3) 20 minutes after initial administration, a supplementary bolus of 4 ug sufentanil was given. The dead space of catheter and filter was 0.6 ml which was first filled with CSF but in subsequent injection, it was filled with the solution of sufentanil, which should be taken into account to adjust the total dosage.

The maternal tympanic temperature was recorded at the time points of baseline, 5, 10, 15 minutes, 1, 2, 3, 4, 5, 6, 7, 8 hours after labor analgesia and 6, 12, 24 hours after delivery. The maternal temperature was measured with a Mon-a-therm tympanic probe (thermistor, YSI400 series, Tyco Healthcare Group LP, Pleasanton, CA, USA; accuracy: ±0.1°C) to elim-

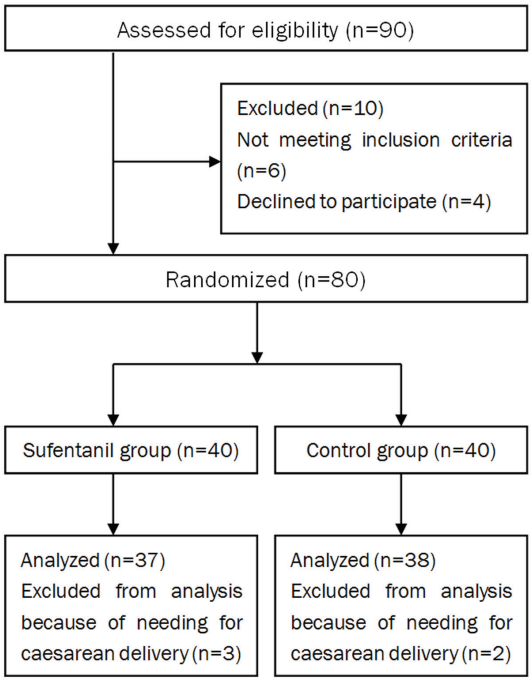

Figure 1. Flow chart of parturient randomized to Sufentanil and control group.

inate the effect of mouth breath and oral intake. The probe was inserted into the right or the left ear canal near the tympanum according to the manufacturer's guidelines. The delivery room temperature was maintained at 21-22°C. Lactated Ringer's solution which was heated to room temperature was intravenous infused before analgesia with 500 ml and maintained at 100 ml/h throughout labor. The number of parturients who developed intrapartum fever (≥38°C) was counted in each group.

Noninvasive blood pressure was measured at regular intervals of 5 minutes, heart rate and arterial oxygen saturation were monitored continuously (AS/5, Datex-Ohmeda monitor, Helsinki, Finland). The data of vaginal examinations, first and second stage durations of labor and analgesia, the number of needing for cesarean section, instrumental delivery, oxytocin augmentation and antibiotic therapy were also collected. The first stage of labor was defined as the time from uterine contraction regular to cervical dilation complete and the second stage was the time from cervical dilation complete to delivery end. The intrapartum antibiotic administration was used routinely in premature rupture of membrane and feverous parturients in our hospital. Side effects such as hypotension, pruritus and post dural puncture headache (PDPH) were abstracted from the medical record. The maternal hypotension, which was defined as systolic arterial pressure <90 mmHg or dropped more than 30% from baseline, was treated with fluid therapy or ephedrine, if necessary. Apgar scores at 1 and 5 minutes, neonatal temperature at the time points of bearing, 6, 12 and 24 hours after the bearing were recorded by a neonatologist to assess the effect of CSLAS on the neonate.

Interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α) were sampled at the time points of the baseline and 5 minutes after delivery. Maternal peripheral venous blood was sampled and centrifuged at 3000 g for 10 minutes within 24 hours, and then the supernatants were stored at -70°C until analysis. Duplicate aliquots of each sample were assayed according to the recommended protocol (Biosource International, Inc, Camarillo, Calif). The standard curves covered the ranges of 0 to 500 pg/ml for IL-6 and TNF-α, 0 to 1000 pg/ml for IL-8. The sensitivities of each assay kit are 2.0 pg/ml for IL-6, 5.0 pg/ml for IL-8 and 1.7 pg/ml for TNF-α, respectively.

Statistical analysis

Continuous variables were described using mean±SD. Qualitative variables were described using relative frequencies expressed as percentages. The primary outcomes were maternal temperature and the VAS score during labor which were analyzed using a longitudinal model. Continuous variables were compared using T test when only two groups involved or ANOVA for more than two groups. Categorical variables were analyzed by the χ^2 test or Fisher's exact test as appropriate. In each case, odds ratios and 95% confidence intervals were calculated from the logistic regression coefficient and standard errors. $P<0.05$ was considered significant difference. All analyses were performed using the software of SPSS 11.0 (Chicago, IL, USA).

Results

90 pregnant women were selected to participate in this research. 10 of the women were excluded at first: 6 did not meet inclusion criteria, 4 declined to participate. 80 women were then randomly assigned to 2 groups with 40 in

Table 1. Maternal demographic and pre-analgesia data (Mean±SD)

Parameter	Sufentanil group	Control group	*P* value*
Age (y)	28.51±2.24	28.21±2.26	0.5617
Weight (kg)	72.57±6.90	73.68±6.36	0.4682
Height (cm)	161.62±4.67	162.68±4.72	0.3303
Duration of pregnancy (w)	39.11±0.88	39.24±0.88	0.5281
Baseline cervical dilatation (cm)	2.73±0.80	2.76±1.08	0.8796
White blood cell count ($\times 10^9$/L)	7.62±1.34	8.04±1.36	0.1810
Neutrophil ($\times 10^9$/L)	72.46±7.67	74.76±5.30	0.1338
VAS before analgesia (mm)	8.30±0.97	8.18±0.80	0.582

Abbreviation: VAS, visual analog scale. *P value of comparison between sufentanil and control groups. P<0.05 means significant difference between the two groups.

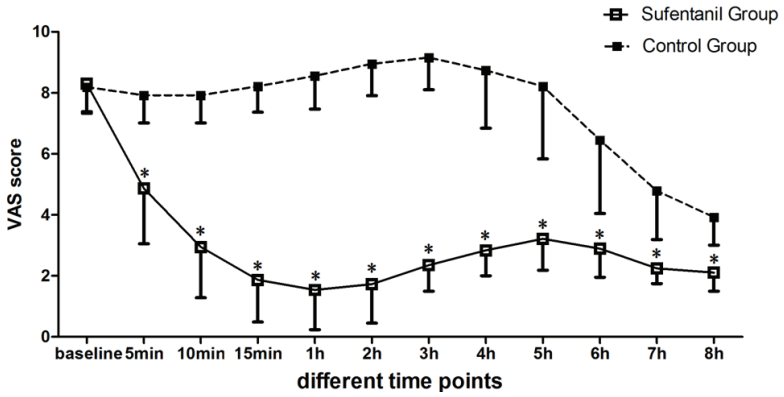

Figure 2. Comparisons of the VAS score at different time points between the two groups. All values represent the means±SD. *P<0.05 Sufentanil Group vs. Control Group.

each. 3 in the sufentanil group and 2 in the control group needed for cesarean delivery and excluded. Finally, 75 women were enrolled in this trial: 37 in the sufentanil group and 38 in the control group (**Figure 1**).

Baseline characteristics such as age, weight, height, cervical dilatation, duration of pregnancy, VAS score, neutrophil and white blood cell count in both groups were with no significant difference (**Table 1**). During the labor procedure, no parturient developed hypotension or hypertension and used vasoactive drug. The heart rate and arterial oxygen saturation were all in the normal range in every parturient.

After intrathecal injection of sufentanil, the sensation of pain was attenuated by a wide margin in sufentanil group compared with the control group. The means of VAS scores were about 1-4 in sufentanil group and 4-9 in control group at different time points which were all significantly different between the two groups. In the control group, the severe pain was reached the highest value of 9.16 at 3 h after CSLAS, compared with 3.22 at 5 h in sufentanil group. In other words, the CSLAS could reduce the sensation of pain and delay the peak sensitivity (**Figure 2**).

With the comparison of women who had a tympanic temperature above 38°C between sufentanil group and control group, the number was 9 in 37 (24.32%) versus 2 in 38 (5.26%), respectively (p=0.024) (**Table 2**). In each group, there was a tendency that maternal temperature elevated gradually with time elapsing from baseline and reached the peak value 5 hours later (38.5°C in sufentanil group, 38.2°C in control group). The changes had statistically significant difference from 3 hours to 7 hours after analgesia compared with baseline (**Figure 3**). The antibiotic usage was 7 patients (18.92%) in the sufentanil group versus 5 patients (13.52%) in the control group (p=0.7525).

The parturients who used sufentanil had a relatively longer time on the second stage of labor than that in the control group which had significant difference (p=0.023). The incidence of pruritus in the sufentanil group was 4 (10.81%) and none in the control group (p=0.038). There were no significant difference in PDPH, the number of vaginal examinations, cesarean section, instrumented delivery and oxytocin augmentation (**Table 2**). Maternal serum IL-6 and IL-8 levels were increased during the labor but with no significant difference between the two

Table 2. Obstetric and neonatal outcomes and analgesia characteristics

Maternal results	Groups		RR	95% CI	*P* value*
	Sufentanil (n=37)	Control (n=38)			
Fever (n/%)	9 (24.32)	2 (5.26)	1.870	1.262-2.772	0.025
Caesarean section (n/%)	3 (7.5)	2 (5)	1.500	0.265-8.504	0.982
Oxytocin augmentation (n/%)	33 (89.19)	32 (84.21)	1.269	0.573-2.814	0.704
Duration of the first stage of labor (median/25-75th percentile)	5 (4-5)	5 (4-5)	_	_	0.397
Duration of the second stage of labor (median/25-75th percentile)	645 (650-770)	635 (380-769)	_	_	0.393
Number of vaginal examinations (median/25-75th percentile)	55 (46-62.5)	49 (44.5-56.25)	_	_	0.027
Instrumental delivery (n/%)	4 (10.81)	4 (10.53)	1.015	0.487-2.116	0.968
Antibiotic usage (n/%)	7 (18.92)	5 (13.52)	1.206	0.700-2.075	0.753
Pruritus (n/%)	4 (10.81)	0 (0)	_	_	0.038
PDPH (n/%)	1 (2.7%)	0 (0)	_	_	0.314
Apgar score (1 min) (median/25-75th percentile)	10 (9-10)	10 (9-10)	_	_	0.582
Apgar score (5 min) (median/25-75th percentile)	10 (9-10)	10 (9-10)	_	_	0.649

Abbreviation: PDPH, post dural puncture headache. *P value of comparison between sufentanil and control groups. P<0.05 means significant difference between the two groups.

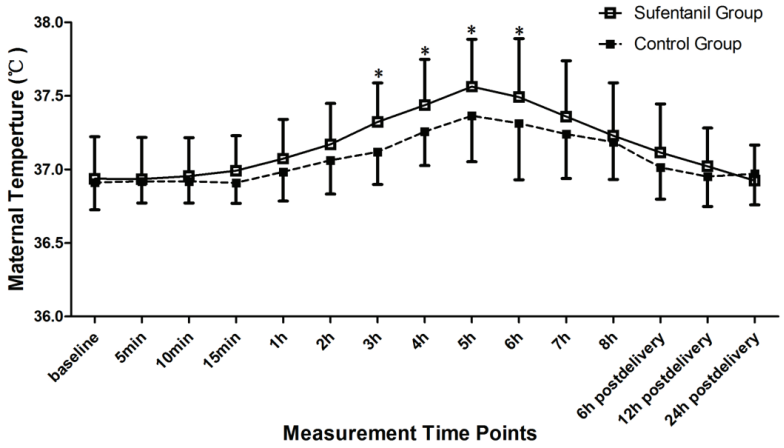

Figure 3. Comparisons of the maternal mean temperature at different time points between the two groups. All values represent the means±SD. *P<0.05 Sufentanil Group vs. Control Group at the time points of 3 h, 4 h, 5 h, and 6 h after labor analgesia.

groups, TNF-α was stable at all time points (**Table 3**).

In relation to neonatal results, median 1 min and 5 min Apgar scores were the same in both groups, the neonatal temperature at the time points of bearing, 6 h, 12 h, 24 h after born were compared and no significant difference was found between the two groups (**Figure 4**). There was no neonate with the temperature above 38°C and administered with antibiotics.

Discussion

Many studies have shown that epidural anesthesia during delivery is associated with an increased risk of maternal fever [4, 12, 13]. And recently, Orange [1] identified that combined spinal-epidural (CSE) anesthesia also played an important role in the elevation of maternal intrapartum temperature; however, no clinical trial has been conducted to clarify the association between CSLAS and maternal fever yet. The present study showed that the rate of fever in sufentanil group was higher than that in the control group which demonstrated that CSLAS had a significant effect on the incidence of fever in parturients.

It has been well recognized that opioids can perform an impact on body temperature in a number of species including human [8, 14-17]. Persistent hypothermia after spinal anesthesia with intrathecal morphine has been described in several studies [18-21]. In our study, it was shown that continuous spinal labor anesthesia with sufentanil induced an increase in maternal

Table 3. Comparisons of maternal cytokine concentrations between the two groups

Parameter	Sufentanil group (Mean±SD)		Control group (Mean±SD)	
	Baseline	5 min after Delivery	Baseline	5 min after Delivery
IL-6 (pg/ml)	5.77±1.50	16.30±2.01*	6.02±1.21	16.51±2.77*
IL-8 (pg/ml)	16.33±2.70	28.02±4.57*	16.72±2.25	29.04±4.19*
TNF-α (pg/ml)	47.09±17.44	47.44±16.86	50.50±20.61	48.36±18.99

*Significant difference to baseline within groups, $P<0.05$. No difference is found between the two groups.

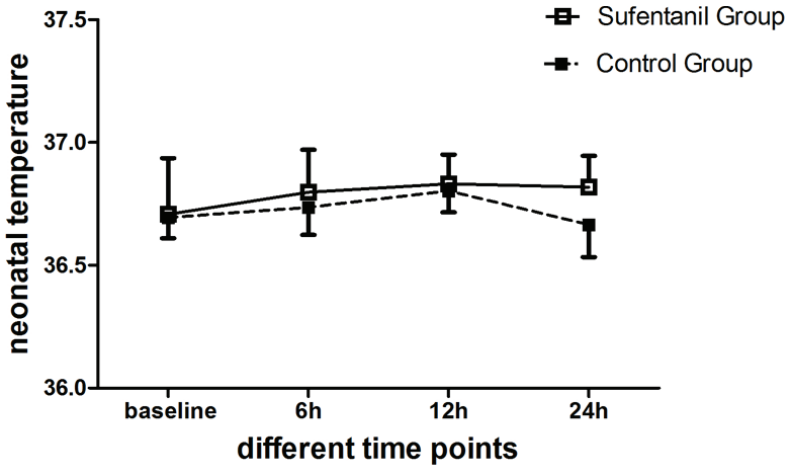

Figure 4. Comparisons of the neonatal mean temperature at different time points between the two groups. All values represent the means±SD. The temperature is not found to be different between the two groups in any time point.

intrapartum temperature, disaccording with the other researchers' results. We interpreted the difference of our results as the women received a different opium drug (sufentanil) with a different method.

The mechanism of this fever is still unclear and the hypothesis that central thermoregulatory response is impaired by regional anesthesia is perhaps the key point [1]. Different opium drugs act on different opium receptors, which are localized within the POA of the anterior hypothalamus, play distinct roles in thermoregulation [17, 22]. The efficacy of sufentanil which is about 1,000 times of morphine [23] has a selective bond and high-affinity to μ_1 site [24]. The μ receptor was reported to have an effect on developing hyperthermia [12, 22]. The method that we administered sufentanil in the space of subarachnoid but not epidural is also a factor. It has rich receptors of temperature sensation and complicated afferent pathways in subarachnoid [25]. The afferent pathways start with primary thermo sensory neurons which generate different temperature sensation by the spino-thalamo-cortical pathway. The variation of temperature in the spinal cord can affect the activity of thermoregulatory neurons in the preoptic area (POA) [26].

Another factor is the dosage of sufentanil that we used 6 ug in bolus, 2 ml/h in maintenance which was smaller than other relevant studies [23]. Other studies showed that systemic administration of opioids primarily generated biphasic effects on body temperature in mouse: developing hyperthermia with low dosage and hypothermia with high dosage [17, 27]. Our research that intrathecal administration of sufentanil with low dosage induced intrapartum fever further proved the results in former studies.

Several studies showed that the increased maternal temperature was not significantly associated with inflammation [28]. On the contrary, others reported that this fever was attributed to infection and epidural techniques could increase the risk of infection. However, these results were based on histological findings alone without the evidence of bacterial culture [12]. IL-6, IL-8 and TNF-α are inflammatory factors which can represent the level of inflammation [15]. In our results, the inflammatory factors of IL-6, IL-8 and TNF-α level in maternal serum were all without significant difference between the two groups, although, the level of IL-6 and IL-8 increased in all parturients irrespectively of groups during the delivery. All of these meant that the CSLAS related fever was not associated with the inflammatory factors as other studies declared [8, 16].

VAS score is a simple and effective scale to measure the level of pain in clinical. We used it

to judge whether the method of CSLAS in labor was practicable and desirable. The result was positive that CSLAS could relieve labor pain by a wide margin compared with the control group. The mean VAS score in sufentanil group was about 3 throughout the labor which represented the satisfaction of parturients was pretty high and it was valuable to popularize to other parturients without contraindication.

The neonatal conditions after born are also important outcomes in our study. We aimed to test the safety of the method CSLAS to neonates. In the sufentanil group, there was no baby developed temperature above 38°C and administered with antibiotics. The Apgar score ranged from 9 to 10 and with no significant difference between two groups. All of these above demonstrated that CSLAS in labor analgesia performed little effect on neonates.

There are some limitations in this study should be mentioned. The procedure of our study was not blind to the participants and doctors because the two groups using a distinct different method which was impossible and with little meaning to be blind. Another one is that although spinal administration of a small dose of sufentanil is safe, there are still potential risks of side effects such as hypotension, pruritus and PDPH. We did not follow up the women with these side effects to analyze the long time effect on parturients. And further studies concerns with CSLAS-associated fever and side effects are to be commended.

In conclusion, the present study shows that CSLAS is a safe and effective method in labor analgesia; however, it is associated with an increased incidence of maternal fever. In the future, well-controlled studies should be conducted to investigate the pathogenesis and prognosis of intrapartum fever by which can we make clear of the mechanism and find effective strategies to control it.

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References

[1] de Orange FA, Passini R Jr, Amorim MM, Almeida T and Barros A. Combined spinal and epidural anaesthesia and maternal intrapartum temperature during vaginal delivery: a randomized clinical trial. Br J Anaesth 2011; 107: 762-768.

[2] Philip JMD, Alexander JM, Sharma SK, Leveno KJ, McIntire DD and Wiley J. Epidural analgesia during labor and maternal fever. Anesthesiology 1999; 90: 1271-1275.

[3] Dashe JS, Rogers BB, McIntire DD and Leveno KJ. Epidural analgesia and intrapartum fever: placental findings. Obstet Gynecol 1999; 93: 341-344.

[4] Segal S. Labor epidural analgesia and maternal fever. Anesth Analg 2010; 111: 1467-1475.

[5] Sharma SK. Epidural analgesia during labor and maternal fever. Curr Opin Anaesthesiol 2000; 13: 257-260.

[6] Macaulay JH, Bond K and Steer PJ. Epidural analgesia in labor and fetal hyperthermia. Obstet Gynecol 1992; 80: 665-9.

[7] Vallejo MC, Kaul B, Adler LJ, Phelps AL, Craven CM, Macpherson TA, Sweet RL and Ramanathan S. Chorioamnionitis, not epidural analgesia, is associated with maternal fever during labour. Can J Anaesth 2001; 48: 1122-1126.

[8] De Jongh RF, Bosmans EP, Puylaert MJ, Ombelet WU, Vandeput HJ and Berghmans RA. The influence of anaesthetic techniques and type of delivery on peripartum serum interleukin-6 concentrations. Acta Anaesthesiol Scand 1997; 41: 853-60.

[9] Anim-Somuah M, Smyth RM and Jones L. Epidural versus non-epidural or no analgesia in labour. Cochrane Database Syst Rev 2011; CD000331.

[10] Sharma SK, Alexander JM, Messick G, Bloom SL, McIntire DD, Wiley J and Leveno KJ. Cesarean delivery: a randomized trial of epidural analgesia versus intravenous meperidine analgesia during labor in nulliparous women. Anesthesiology 2002; 96: 546-551.

[11] Petrova A, Demissie K, Rhoads GG, Smulian JC, Marcella S and Ananth CV. Association of

maternal fever during labor with neonatal and infant morbidity and mortality. Obstet Gynecol 2001; 98: 20-27.
[12] Riley LE, Celi AC, Onderdonk AB, Roberts DJ, Johnson LC, Tsen LC, Leffert L, Pian-Smith MC, Heffner LJ, Haas ST and Lieberman ES. Association of epidural-related fever and noninfectious inflammation in term labor. Obstet Gynecol 2011; 117: 588-595.
[13] Thierrin L and Mercier F. Epidural analgesia and fever during labor. J Gynecol Obstet Biol Reprod (Paris) 2005 Sep; 34: 423-6.
[14] Baker A and Meert T. Morphine and d-amphetamine nullify each others' hypothermic effects in mice. Pharmacol Toxicol 2003; 92: 64-70.
[15] Mantha VR, Vallejo MC, Ramesh V, Jones BL and Ramanathan S. Maternal and cord serum cytokine changes with continuous and intermittent labor epidural analgesia: a randomized study. ScientificWorldJournal 2012; 2012: 607938.
[16] Goetzl L, Evans T, Rivers J, Suresh MS and Lieberman E. Elevated maternal and fetal serum interleukin-6 levels are associated with epidural fever. Am J Obstet Gynecol 2002; 187: 834-838.
[17] Baker AK and Meert TF. Functional effects of systemically administered agonists and antagonists of mu, delta, and kappa opioid receptor subtypes on body temperature in mice. J Pharmacol Exp Ther 2002; 302: 1253-1264.
[18] Peillon P, Dounas M, Lebonhomme JJ and Guittard Y. [Severe hypothermia associated with cesarean section under spinal anesthesia]. Ann Fr Anesth Reanim 2002; 21: 299-302.
[19] Sayyid SS, Jabbour DG and Baraka AS. Hypothermia and excessive sweating following intrathecal morphine in a parturient undergoing cesarean delivery. Reg Anesth Pain Med 2003; 28: 140-143.
[20] Hess PE, Snowman CE and Wang J. Hypothermia after cesarean delivery and its reversal with lorazepam. Int J Obstet Anesth 2005; 14: 279-283.
[21] Fischer MO, Dequire PM, Kalem A, Gerard JL and Plaud B. [Hypothermia after spinal anaesthesia: implication of morphine?]. Ann Fr Anesth Reanim 2006; 25: 296-298.
[22] Salmi P, Kela J, Arvidsson U and Wahlestedt C. Functional interactions between delta- and mu-opioid receptors in rat thermoregulation. Eur J Pharmacol 2003; 458: 101-106.
[23] Sevarino FB, Johnson MD, Lema MJ, Datta S, Ostheimer GW and Naulty JS. The effect of epidural sufentanil on shivering and body temperature in the parturient. Anesth Analg 1989; 68: 530-533.
[24] Höcker J, Weber B, Tonner PH, Scholz J, Brand PA, Ohnesorge H and Bein B. Meperidine, remifentanil and tramadol but not sufentanil interact with α2-adrenoceptors in α2A-, α2B- and α2C-adrenoceptor knock out mice brain. Eur J Pharmacol 2008; 582: 70-77.
[25] Romanovsky AA. Thermoregulation: some concepts have changed. Functional architecture of the thermoregulatory system. Am J Physiol Regul Integr Comp Physiol 2007; 292: R37-46.
[26] Kahn SA, Beers RJ and Lentz CW. Do fentanyl and morphine influence body temperature after severe burn injury? J Burn Care Res 2011; 32: 309-316.
[27] Ryan KF, Price JW, Warriner CB and Choi PT. Persistent hypothermia after intrathecal morphine: case report and literature review. Can J Anaesth 2012; 59: 384-8.
[28] Wang LZ, Hu XX, Liu X, Qian P, Ge JM and Tang BL. Influence of epidural dexamethasone on maternal temperature and serum cytokine concentration after labor epidural analgesia. Int J Gynaecol Obstet 2011; 113: 40-43.