Intrathecal Sufentanil and Fetal Heart Rate Abnormalities: A Double-Blind, Double Placebo-Controlled Trial Comparing Two Forms of Combined Spinal Epidural Analgesia with Epidural Analgesia in Labor

M. Van de Velde, MD, PhD*, A. Teunkens, MD*, M. Hanssens, MD, PhD, FRCOG†, E. Vandermeersch, MD, PhD*, and J. Verhaeghe, MD, PhD†

Departments of *Anesthesiology and †Obstetrics and Gynecology, University Hospitals Gasthuisberg, Katholieke Universiteit Leuven, Herestraat, Belgium

Combined spinal epidural analgesia (CSE) for labor pain relief has become increasingly popular. However, the effect of intrathecal sufentanil on the incidence of uterine hyperactivity and fetal heart rate (FHR) abnormalities remains controversial. We hypothesized that the use of intrathecal sufentanil in a dose of 7.5 μg is more likely to induce a nonreassuring FHR tracing than a small dose of spinal sufentanil combined with bupivacaine or epidural analgesia. Three-hundred parturients were randomized into three groups. In the first group, epidural analgesia was initiated with 12.5 mg of bupivacaine, 12.5 μg of epinephrine, and 7.5 μg of sufentanil in a volume of 10 mL (EPD group). In Group 2, initial intrathecal analgesia consisted of 2.5 mg of bupivacaine, 2.5 μg of epinephrine, and 1.5 μg of sufentanil (BSE group); in Group 3, spinal analgesia consisted of 7.5 μg of sufentanil (SUF group). Analgesia was maintained in all groups with patient-controlled epidural analgesia using bupivacaine 0.125%, 1.25 μg/mL of epinephrine, and 0.75 μg/mL of sufentanil (bolus, 4 mL; lockout, 15 min). Cardiotocography was monitored continuously 15 min before analgesia and for 60 min after the start of analgesia. The quality of analgesia, labor, and neonatal outcome and side effects were recorded. Twenty-four percent of patients in the SUF group developed FHR abnormalities (bradycardia or late decelerations) during the first hour after initiation of analgesia compared with 12% in the BSE group and 11% in the EPD group. Uterine hyperactivity occurred in 12% of parturients in the SUF group but in only 2% in the other groups. Onset of analgesia was more rapid in both CSE groups as compared with the EPD group. However, 29% of patients in the BSE group developed severe hypotension, requiring IV ephedrine (29% in the BSE group versus 7% and 12% in the EPD and SUF groups, respectively). All these differences reached statistical significance. The present data corroborate previous recommendations of caution when performing CSE using a large dose (7.5 μg or more) of spinal sufentanil because of the risk of uterine hyperactivity and FHR abnormalities.

(Anesth Analg 2004;98:1153–9)

Combined spinal epidural analgesia (CSE) to relieve labor pain has become increasingly popular in recent years (1,2). CSE produces effective analgesia with rapid onset and minimal motor impairment (1–3). Anesthetic requirements are significantly reduced as compared with the dose used in epidural analgesia (4).

Nonreassuring fetal heart rate (FHR) abnormalities have been reported after the injection of spinal opioids in parturients with an arterial blood pressure that was stable and within normal limits (5,6). Nonreassuring FHR patterns caused by spinal opioids were reported by some to be associated with uterine hyperactivity (5,6). There is no agreement on this issue. Norris (7) concluded that there is insufficient evidence to accept that spinal opioids are responsible for a more frequent incidence of new FHR abnormalities, as compared with conventional epidural analgesia. Mardirosoff et al. (8) came to the opposite conclusion after performing a meta-analysis comparing spinal opioid analgesia with either spinal bupivacaine or epidural analgesia. These authors concluded that intrathecal opioids are

Accepted for publication October 3, 2003.

Address correspondence and reprint requests to Marc Van de Velde, MD, PhD, Director Obstetric Anesthesia and Extra Muros Anesthesia, Department of Anesthesiology, University Hospitals Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium. Address e-mail to marc.vandevelde@uz.kuleuven.ac.be.

DOI: 10.1213/01.ANE.0000101980.34587.66

0003-2999/04

associated with the occurrence of fetal bradycardia. In a retrospective survey of 1293 cases of regional labor analgesia, significantly more nonreassuring cardiotocographic tracings with spinal sufentanil 7.5 μg were recorded than with either conventional epidural analgesia or CSE analgesia with bupivacaine and 1.5 μg of sufentanil (6).

There have been no large randomized, placebo-controlled trials specifically designed to evaluate the incidence of nonreassuring FHR patterns using different anesthetic techniques (with or without spinal opioids). We designed a double-blind, double placebo-controlled study to determine whether the use of intrathecal sufentanil in a dose of 7.5 μg has a higher risk of inducing a nonreassuring FHR tracing than a small dose of spinal sufentanil or epidural analgesia.

Methods

After ethical committee approval and written patient-informed consent, 300 full term (>37 wk) ASA physical status I or II parturients in labor were recruited to participate in this double-blind, double placebo-controlled trial. All women had uncomplicated, vertex presenting, singleton pregnancies and requested regional analgesia. Patients were at least 18 yr of age, and those carrying a fetus with known or suspected congenital abnormalities were excluded. Maternal age, height, weight, cervical dilation, gestational age, type of labor, status of the membranes, use of oxytocin, and medical history were recorded. The FHR was recorded for 15 min before analgesia using external cardiotocography. Maternal arterial blood pressure and heart rate during the last antenatal visit and just before analgesia were noted. Pain was assessed using a visual analog scale (VAS; 100 mm; 0 = no pain and 100 = worst pain imaginable) and recorded 10 min before the CSE.

Before initiation of the regional block, a fluid load consisting of Ringer's lactated solution in a dose of 10 mL/kg was administered IV. The epidural space was identified at the L3-4 or L4-5 interspace with an 18-gauge Tuohy needle using the loss of resistance to saline technique with the patient sitting. A 29-gauge pencil-point spinal needle perforated the dura via the Tuohy needle. When free-flowing, cerebrospinal fluid was obtained, the spinal study solution (2 mL) was injected intrathecally. The spinal needle was then removed, and the epidural study solution (10 mL) was injected through the epidural needle. A 20-gauge epidural catheter was positioned 4 cm in the epidural space. No epidural test-dose was given. If the epidural or subarachnoid space could not be identified, the mother was excluded from the study.

Parturients were randomized, in a double-blind fashion, using a computer-generated list. Patients were allocated to one of three study groups, each of 100 patients. Randomization was stratified on whether the woman was nulliparous or not. Stratification resulted in equal distribution of nulliparous and multiparous women in each study group.

For each study group, the hospital's pharmacist prepared serially numbered packets containing two blinded, sterile syringes. A first syringe contained 2 mL of the initial spinal solution, and a second syringe contained 10 mL of the initial epidural solution, which was administered through the Tuohy needle. In the first group (EPD group), the spinal solution contained plain saline, whereas the epidural solution contained 10 mL of bupivacaine 0.125% with sufentanil 0.75 μg/mL and 12.5 μg epinephrine. In the second group (BSE group), the spinal solution contained 1.5 μg of sufentanil, 2.5 μg of epinephrine and 2.5 mg of bupivacaine, whereas the epidural solution contained plain saline. In the third group (SUF group), the spinal solution consisted of sufentanil 7.5 μg, and the epidural solution contained 10 mL of plain saline.

If pain relief was inadequate (VAS score for pain >20 mm) 20 min after the initiation of CSE, a further 10 mL of epidural bupivacaine 0.125% with sufentanil 0.75 μg/mL and 1.25 μg/mL epinephrine was given. If pain relief remained inadequate 20 min later, 5 mL of lidocaine 2% was given. If sufficient pain relief was achieved within 20 min, the study continued. However, if pain relief remained inadequate, the patient was withdrawn, and alternative analgesic strategies were presented to the patient, or the epidural catheter was re-sited.

Analgesia was maintained using patient-controlled epidural analgesia using 4 mL of bupivacaine 0.125% with sufentanil 0.75 μg/mL and 1.25 μg/mL epinephrine and a lockout of 15 min without a continuous background infusion. The patient-controlled epidural analgesia device was started immediately after the first request for additional pain relief.

The primary outcome variables were the occurrence of new nonreassuring FHR abnormalities or uterine hyperactivity. FHR abnormalities considered were late decelerations (FHR <100 bpm after a contraction) or bradycardia (FHR <100 bpm for more than 90 s). FHR tracings were assessed by the attending obstetrician blinded to the patient group randomization. Uterine activity was evaluated using external tocography in combination with clinical assessment by the attending obstetrician. The presence or absence of uterine hyperactivity was recorded based on external tocography and clinical evaluation. Cardiotocographic recordings were continuously performed for 15 min before and 60 min after the CSE.

If FHR abnormalities occurred, conservative measures were taken (left lateral decubitus, oxygen by face mask, IV fluids, cessation of IV oxytocin, and, in case of hypotension, administration of IV ephedrine). The

attending obstetrician made the decision as to whether or not to administer a tocolytic drug (ritodrine, 10 mg IV). Cesarean delivery was performed if fetal bradycardia persisted for more then 10 min or if additional diagnostic testing (fetal scalp blood gas analysis or fetal pulse oximetry) suggested signs of fetal hypoxia.

A pain score was recorded for each contraction until the VAS score was <20 mm for 2 consecutive contractions. Onset time of analgesia was defined as the time between the end of the spinal injection and the moment the VAS score was <20 mm. Pain was also assessed at 5, 10, 20, 30, 40, 50, 60, and 90 min after the end of the spinal injection and every 60 min up until delivery. In addition, pain was assessed at the moment the patient requested additional analgesia and at full cervical dilation. The duration of initial analgesia was defined as the time between the end of the spinal injection and the moment additional analgesia was requested. Overall quality of pain relief was recorded 60 min after delivery of the baby using the VAS score (0 = completely unsatisfied and 100 = completely satisfied).

Sensory block, motor block, maternal heart rate and arterial blood pressure, FHR and the presence of pruritus, and nausea/vomiting were regularly recorded. Motor block was measured using a six-point scale with 1 = no motor impairment, 2 = weak hip flexion, 3 = weak knee extension, 4 = weak knee flexion, 5 = weak foot dorsiflexion, and 6 = weak foot plantar flexion. A sustained leg lift (SLL) was performed at the moment the VAS score for pain was <20 mm. In the supine position and with closed eyes, the parturient was requested to maintain a 45-degree hip flexion with an extended knee for 45 s for each leg separately. If she successfully performed this test with both legs, the SLL was judged positive. If no motor impairment was noted at a VAS <20 mm and the SLL was positive, the mothers were allowed to ambulate. Maternal hypotension (a decrease of mean arterial blood pressure of >10% from prelabor baseline) was recorded. If maternal hypotension was severe (a decrease of mean arterial blood pressure of >15% from prelabor baseline), IV ephedrine in 5- or 10-mg increments was given until arterial blood pressure returned within a 10% margin of prelabor values. Prelabor arterial blood pressures were measured during the last antenatal visit.

The total and hourly dose of bupivacaine was noted. Outcome of labor was recorded. Neonatal outcome was assessed using Apgar scores at 1 and 5 min after birth, and umbilical artery blood gases at birth and admittance to the neonatal intensive care unit were noted. The occurrence of postdural puncture headache (PDPH) was registered.

Continuous variables were statistically analyzed using analysis of variance and Scheffé *post hoc* test whenever appropriate. Categorical data were analyzed using the Fisher's exact test and χ^2 analysis. $P < 0.05$ was considered significant. Data are presented as mean ± SD, percentage of group total, or median with interquartile range.

Results

From 300 enrolled parturients, 4 were withdrawn. In three patients, the spinal space could not be identified (spinal failure rate, 1%), and in one mother, the epidural catheter did not produce analgesia within 60 min (epidural failure rate, 0.33%). Of these four patients, two belonged to the SUF group and two to the BSE group. The SUF group contained 98, the BSE group 98, and the EPD group 100 patients for final analysis.

No demographic differences were observed among the groups (Table 1). The groups were similar with respect to parity, mean gestational age, mean cervical dilation at entry, the percentage of induced labors, the percentage of ruptured membranes at entry, the percentage of oxytocin augmented labors, oxytocin use, hourly cervical dilation, and the duration of labor (Table 1). In the SUF group, significantly less cesarean deliveries were performed. However, the number of cesarean deliveries performed for nonreassuring FHR was the same among the groups (4 versus 4 versus 3 in the EPD, BSE, and SUF groups, respectively). In none of these patients was a decision made to perform an emergency caesarean delivery within the first hour after initiation of analgesia.

Nonreassuring FHR patterns were significantly more common after intrathecal sufentanil 7.5 μg when compared with both other types of analgesia (24% versus 11%, and 12% in the EPD and BSE groups, respectively; $P < 0.05$; Table 2). In the SUF group, the diagnosis of uterine hyperactivity was made significantly more often than in the other groups (12% versus 2%, and 2% in the epidural and BSE groups, respectively; $P < 0.05$; Table 2). However, tocolytic therapy was rarely required because most episodes resolved with conservative measures such as IV fluids, oxygen, and left lateral decubitus (Table 2). Maternal hypotension (>10% reduction of mean arterial blood pressure) occurred in approximately one-third of the women in all 3 groups (31%, 33%, and 33% in the EPD, BSE, and SUF groups, respectively; Table 2). Severe hypotension (>15% reduction in mean arterial blood pressure) was more common in the BSE group (7%, 29%, and 12% in the EPD, BSE, and SUF groups, respectively; $P < 0.05$; Table 2), and the dose of ephedrine to treat hypotension was larger in the BSE group than in either of the other groups (Table 2). There was no correlation between hypotension and the occurrence of nonreassuring FHR abnormalities.

Onset of analgesia was significantly shorter in the SUF and BSE groups when compared with the EPD

Table 1. Demographic and Obstetric Data

	EPD group (n = 100)	BSE group (n = 98)	SUF group (n = 98)
Age (yr)	29 (27–32)	29 (27–33)	29 (26–32)
Height (cm)	165 ± 6	171 ± 6	166 ± 6
Weight (kg)	78 ± 12	78 ± 13	81 ± 13
Gestational age (wk)	39.7 ± 1.3	39.5 ± 1.2	39.7 ± 1.2
Cervical dilation at entry (cm)	3.4 ± 1.4	3.7 ± 1.5	3.5 ± 1.2
Induced labors (%)	71	66	65
Ruptured membranes at entry (%)	66	65	67
Labors with oxytocin (%)	45	52	48
Cervical dilation (cm/h)	2.6 ± 1.4	2.7 ± 1.5	2.5 ± 1.5
Duration 1st stage (min)	160 (115–227)	150 (90–247)	195 (120–270)
Duration 2nd stage (min)	25 (13–37)	25 (12–50)	20 (11–40)
Cesarean delivery (%)	13	17	4*
Instrumental delivery (%)	16	13	21

Results are presented as mean ± SD, median (interquartile range), or as % of group total.
* $P < 0.05$ versus BSE- and EPD-groups.
EPD = epidural; BSE = bupivacaine + epinephrine + sufentanil; SUF = sufentanil.

Table 2. Data Related to Nonreassuring Fetal Heart Rate, Uterine Hyperactivity, Maternal Hypotension, and Ephedrine Treatment

	EPD group (n = 100)	BSE group (n = 98)	SUF group (n = 98)
Nonreassuring fetal heart rate (%)	11	12	24*
Uterine hyperactivity (%)	2	2	12†
Tocolysis (%)	0	2	1
Hypotension (%)	31	33	33
Ephedrine treatment (%)	7	29‡	12
Ephedrine (mg)	0 (0–0)	0 (0–5)	0 (0–0)

Results are presented as mean ± SD, median (interquartile range), or as % of group total.
* $P < 0.05$ versus epidural (EPD) groups; † $P < 0.05$ versus bupivacaine + epinephrine + sufentanil (BSE-) and EPD-groups; ‡ $P < 0.05$ versus (SUF-) sufentanil and EPD-group.

group (268 ± 114 versus 321 ± 183 versus 1035 ± 754 s in the BSE, SUF, and EPD groups, respectively; $P < 0.05$; Table 3). During the first 30 min, the VAS scores for pain were less in the SUF and BSE groups (Fig. 1). The duration of initial spinal analgesia was comparable among the groups (Table 3). Although maternal and midwifery VAS scores for analgesic satisfaction were similar among the groups, more parturients scored their analgesia as excellent in the BSE group than in the EPD group and SUF group (Table 3). In the SUF and BSE groups, bupivacaine consumption was less than in the EPD group (Table 3).

Neonatal outcome was comparable among the groups (Table 4). In the EPD group, significantly more motor block was observed, and more women in the SUF and BSE groups were able to ambulate after initial analgesia and never experienced motor block throughout labor (Table 5). Less pruritus was observed in the EPD group (Table 5). No case of PDPH was observed.

Discussion

The present randomized, double-blind, double placebo-controlled trial compared the effect of three techniques of neuraxial labor analgesia on FHR and confirmed the results of a previously published retrospective investigation (6). Intrathecal sufentanil in a dose of 7.5 μg is associated with a more frequent incidence of nonreassuring FHR patterns when compared with epidural analgesia with a combination of local anesthetic, opioids, and epinephrine or CSE analgesia using a smaller dose of spinal sufentanil combined with bupivacaine.

The effect of intrathecal opioids on FHR has remained a controversial topic in obstetric anesthesia. Eltzschig et al. (9) warned against the risk of abnormal FHR patterns after CSE analgesia. Late decelerations, as well as fetal bradycardia, have been reported (5,6), but several large series were unable to confirm an increased risk using spinal opioids (10,11). Norris (7) reviewed the literature and concluded that "the preponderance of existing evidence suggests that a similar risk of fetal bradycardia exists when inducing labor analgesia with intrathecal opioids as compared to epidural analgesia." In contrast, Mardirosoff et al. (8), having performed a meta-analysis of published, randomized trials, concluded that intrathecal opioids increase the risk of fetal bradycardia as compared with nonintrathecal analgesia.

The present trial confirms that spinal sufentanil carries a higher risk of inducing FHR abnormalities but suggests that the risk is apparently related to the dose of sufentanil administered. In this trial, smaller intrathecal doses of sufentanil (combined with local anesthetics) did not result in a more frequent incidence of FHR abnormalities, despite equally rapid pain relief and a more frequent incidence of severe hypotension. This is in agreement with the findings of Vercauteren

Table 3. Data on Analgesia

	EPD group (n = 100)	BSE group (n = 98)	SUF group (n = 98)
Onset time (seconds)	1035 ± 754	268 ± 114*	321 ± 183*
Duration 1st dose (min)	85 ± 53	82 ± 29	75 ± 34
VAS satisfaction mother (mm)	90 ± 14	93 ± 11	91 ± 11
VAS satisfaction midwife (mm)	90 ± 13	92 ± 12	90 ± 11
Satisfaction-score: excellent (%)	70	90*	78†
Total bupivacaine consumption (mg)	41 ± 22	30 ± 22*	31 ± 19*
Hourly bupivacaine consumption (mg/h)	12.3 ± 5.4	8.9 ± 4.3*	8.1 ± 3.5*

Results are presented as mean ± SD or as % of group total.
VAS = visual analogue scale; EPD = epidural; BSE = bupivacaine + epinephrine + sufentanil; SUF = sufentanil.
* $P < 0.05$ versus EPD group; † $P < 0.05$ versus BSE group.

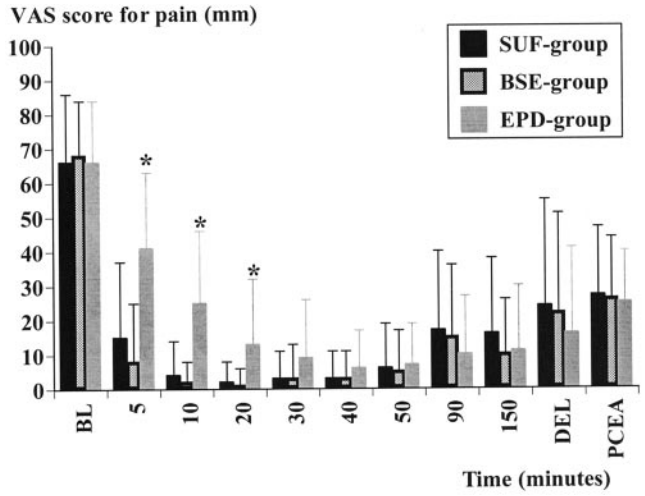

Figure 1. Visual analog scale (VAS) score for pain. *$P < 0.05$ versus SUF and BSE groups. BL = baseline; DEL = delivery; PCEA = patient-controlled epidural analgesia (first request for additional analgesia).

et al. (12), who previously demonstrated that intrathecal sufentanil 7.5 μg caused cardiotocographic abnormalities more often than 1.35 μg. Further studies are required to confirm a dose-response relationship between intrathecal sufentanil and FHR abnormalities.

The presumed mechanism of opioid-induced nonreassuring FHR tracings is uterine hyperactivity caused by rapid onset of analgesia, leading to an imbalance in the type of maternal circulating catecholamines (5). Based on laboratory investigations, increased myometrial tone and increased uterine vascular resistance may be caused by the decrease of epinephrine levels in the continuing presence of high norepinephrine levels associated with the sudden onset of pain relief (13). Although the present trial suggests a role of uterine hyperactivity, it does not support the above-described mechanism because equally fast analgesia was produced after CSE using a mixture of bupivacaine and a small dose of sufentanil, without inducing more FHR abnormalities. We can only speculate about alternative pathophysiological mechanisms. It is known from animal and human studies that IV and intrathecal opioids have central effects and can alter the release of various central peptides, including oxytocin and vasopressin (14–16). Further study into the mechanism is required.

It is important to note that all study drugs were prepared by the pharmacist so that the risk of drug errors in this study was limited. Many anesthesiologists believe that previous reports of FHR abnormalities may relate to errors in drug mixing and the dose of opioids. Our results do not support this assumption.

Uterine activity was assessed using external cardiotocography and clinical judgment by the attending obstetrician. Intrauterine tocometry would have been more accurate to diagnose uterine hyperactivity. However, this would have excluded all women without ruptured membranes and would have resulted in difficulties recruiting patients.

The present trial does not show any evidence indicating worse neonatal outcome after a large dose of intrathecal sufentanil based on relatively crude measures such as Apgar scores, umbilical artery blood gas analysis, and admittance to the neonatal intensive care unit. This is in accordance with previous reports (5,6,9–11,17). In none of these reports was there a need for emergency Cesarean deliveries as a result of sufentanil-induced nonreassuring FHR tracings (5,6,9–11). Only Gambling et al. (17) have reported an increased cesarean delivery rate caused by more nonreassuring FHR patterns, but here, also, neonatal outcome was good and did not differ from the control group. However, Gambling et al. did not record FHR tracings before initiation of analgesia in the control group and may have missed continuing FHR abnormalities.

The value of FHR monitoring to predict adverse neonatal outcome has been questioned (18). Furthermore, it has been demonstrated that continuous FHR monitoring as compared with intermittent auscultation does not improve outcome. On the contrary, continuous FHR monitoring has led to more operative vaginal deliveries and cesarean deliveries (19,20).

Table 4. Neonatal Outcome Data

	EPD group (n = 100)	BSE group (n = 98)	SUF group (n = 98)
Apgar score < 7 (%)	7	5	7
Umbilical artery pH < 7.2 (%)	21	14	17
Umbilical artery pH < 7.1 (%)	3	1	4
Umbilical artery pH	7.26 ± .08	7.27 ± .06	7.26 ± .07
Umbilical artery po_2 (mm Hg)	16.6 ± 6.0	16.7 ± 5.9	17.4 ± 5.9
Umbilical artery pco_2 (mm Hg)	56.0 ± 10.4	53.8 ± 8.2	54.0 ± 9.0
Umbilical artery HCO^{3-}	21.1 ± 3.4	21.7 ± 2.9	21.1 ± 3.1
Umbilical artery base excess	−3.0 ± 3.1	−2.8 ± 2.9	−2.8 ± 2.7

Results are presented as mean ± SD or as % of group total. No statistically significant differences were observed.

Table 5. Maternal Functional Tests and Side Effects

	EPD group (n = 100)	BSE group (n = 98)	SUF group (n = 98)
No motor impairment at VAS < 20 mm (%)	81	91*	94*
Sustained leg lift positive at VAS < 20 mm (%)	69	83*	88*
Ability to be mobile at VAS < 20 mm (%)	66	82*	86*
No motor impairment during labor (%)	63	80*	82*
Pruritus (%)	24	58*†	88*
Nausea (%)	5	8	5

Results are presented as mean ± SD or as % of group total.
VAS = visual analogue scale; EPD = epidural; BSE = bupivacaine + epinephrine + sufentanil; SUF = sufentanil.
* $P < 0.05$ versus EPD group; † $P < 0.05$ versus SUF group.

However, despite these concerns, FHR monitoring remains the clinical standard for fetal surveillance during labor (21).

In the present investigation, a small incidence of cesarean delivery for dystocia was observed in patients treated with pure intrathecal sufentanil. This was counteracted by more instrumental vaginal deliveries, resulting in a similar spontaneous delivery rate among the groups. Because obstetric management was not standardized in the present investigation, the differences may relate to differences in obstetric practice between different obstetricians despite randomization. Although motor block was significantly more pronounced in women randomized to receive an epidural, no differences in motor impairment were observed between the two CSE groups. It is therefore unlikely that differences in maternal motor power would account for the observed differences in cesarean delivery rate. The reduction in motor impairment by both CSE techniques is important; however, this is not a universal finding in previous studies comparing CSE and epidural analgesia (3,4,22). Of note, maintenance of analgesia was similar in the 3 study groups. In previous comparative trials, conclusions on motor power effects were often clouded by the fact that different maintenance regimens were used among the CSE and epidural groups.

The present study also provides additional information on the potential advantages of CSE analgesia in labor. As in previous investigations, significantly faster onset of analgesia, increased patient satisfaction, and less local anesthetic consumption were observed in the CSE groups (1,4). The latter was mainly because of the omission of the initial epidural dose. However, our study was not specifically designed to evaluate local anesthetic-sparing effects of the initial spinal dose on further epidural top ups. Furthermore, it would be difficult to evaluate this in our setting because mean duration of labor after initiation of analgesia was approximately 3.5 h. However, the dose-sparing effects were clinically relevant because less motor block was observed.

Surprisingly, CSE using a combination of bupivacaine and sufentanil did not result in more prolonged analgesia as compared with pure intrathecal sufentanil analgesia. This is in contrast to Campbell et al. (23), who observed significantly longer analgesia when intrathecal sufentanil was combined with bupivacaine, as compared with the two drugs separately. Of note is in the latter study, patients in both the pure sufentanil CSE group and the combination CSE group received 10 μg of spinal sufentanil. In the present investigation, the sufentanil dose was different between the BSE and SUF groups, using less sufentanil in the combination group. This may account for the observed differences in duration of spinal analgesia.

More severe hypotension occurred in the BSE group, but this did not produce more FHR abnormalities and was easily treated. The administration of epidural saline in the CSE groups may have affected the spinal spread of intrathecally administered drugs by epidural volume expansion (24–26). Although we

did not record block levels in the present trial, epidural volume expansion may have affected cephalad spread in the CSE groups and resulted in a higher block. Together with the use of local anesthetics in the BSE group, this might account for more pronounced hypotension.

It can be argued that intentional perforation of the dura to administer intrathecal saline (as in the EPI group) is unethical. However, we previously showed that the incidence of PDPH resulting solely from the spinal needle in a CSE technique is 0.1%. In the present trial, there were no cases of PDPH. Using a CSE technique also has the advantage of producing fewer dysfunctional epidural catheters (27). The intentional perforation of the dura to administer saline may have resulted in the spinal spread of epidurally administered local anesthetics (23). Although this makes our CSE and EPD groups far from standard, we feel this did not affect our primary outcome goals.

We conclude that CSE for labor pain relief using 7.5 μg of intrathecal sufentanil results in a more frequent incidence of nonreassuring FHR recordings and uterine hyperactivity but does not result in serious maternal and neonatal morbidity. The results of the present investigation argue against the hypothesis that the onset of rapid analgesia is the most important causative factor linking intrathecal opioids to uterine hyperactivity and FHR abnormalities. We believe that other mechanisms are involved that require further investigation. Additionally, studies designed to evaluate the dose-response relationship between sufentanil and nonreassuring FHR abnormalities should be performed.

The authors wish to express their sincere gratitude to the midwifery staff of the University Hospitals Gasthuisberg, Leuven, for their excellent and enthusiastic cooperation in this randomized clinical trial. Without their midwifery expertise and persistent enthusiasm, the present study would never have been accomplished. The authors also express their gratitude to Dr. Liesbeth Hutsebaut, D. Pharm, and her motivated staff for the production and randomization of study drugs. The authors wish to express their sincere gratitude to Dr. Ariane Kumar, MB, BS, for revision of our manuscript.

References

1. Stacey RG, Watt S, Kadim MY, Morgan BM. Single space combined spinal epidural technique for analgesia in labour. Br J Anaesth 1993;71:499–502.
2. Collis RE, Davies DWL, Aveling W. Randomised comparison of combined spinal-epidural and standard epidural analgesia in labour. Lancet 1995;345:1413–6.
3. Kartawiadi SL, Vercauteren MP, Van Steenberghe AL, Adriaensen HA. Spinal analgesia during labor with low-dose bupivacaine, sufentanil, and epinephrine. Reg Anesth 1996;21:191–6.
4. Van de Velde M, Mignolet K, Vandermeersch E, Van Assche A. Prospective, randomized comparison of epidural and combined spinal epidural analgesia during labor. Acta Anaesthesiol Belg 1999;50:129–36.
5. Clarke VT, Smiley RM, Finster M. Uterine hyperactivity after intrathecal injection of fentanyl for analgesia during labor: a cause of fetal bradycardia? Anesthesiology 1994;81:1083.
6. Van de Velde M, Vercauteren M, Vandermeersch E. Fetal heart rate abnormalities after regional analgesia for labor pain: the effect of intrathecal opioids. Reg Anesth Pain Med 2001;26:257–62.
7. Norris MC. Intrathecal opioids and fetal bradycardia: is there a link? Internatl J Obstet Anesth 2000;9:264–9.
8. Mardirosoff C, Dumont L, Boulvain M, Tramer MR. Fetal bradycardia due to intrathecal opioids for labour analgesia: a systematic review. Br J Obstet Gynaecol 2002;109:274–81.
9. Eltzschig HK, Lieberman ES, Camann WR. Regional anesthesia and analgesia for labor and delivery. N Engl J Med 2003;348:319–32.
10. Nielsen PE, Erickson JR, Abouleish EI, et al. Fetal heart rate changes after intrathecal sufentanil or epidural bupivacaine for labor analgesia: incidence and clinical significance. Anesth Analg 1996;83:742–6.
11. Palmer CM, Maciulla JE, Cork RC, et al. The incidence of fetal heart rate changes after intrathecal fentanyl labor analgesia. Anesth Analg 1999;88:577–81.
12. Vercauteren M, Bettens K, Van Springel G, et al. Intrathecal labor analgesia: can we use the same mixture as is used epidurally? Internatl J Obstet Anesth 1997;6:242–6.
13. Segal S, Csavoy AN, Datta S. The tocolytic effect of catecholamines in the gravid rat uterus. Anesth Analg 1998;87:864–9.
14. Ummenhofer WC, Arends RH, Shen DD, Bernards CM. Comparative spinal distribution and clearance kinetics of intrathecally administered morphine, fentanyl, alfentanil and sufentanil. Anesthesiology 2000;92:739–53.
15. Russel JA, Gosden RG, Humphreys EM, et al. Interruption of parturition in rats by morphine: a result of inhibition of oxytocin secretion. J Endocrinol 1989;121:521–36.
16. Stocche RM, Klamt JG, Antunes-Rodrigues J, et al. Effects of intrathecal sufentanil on plasma oxytocin and cortisol concentrations in women during the first stage of labor. Reg Anesth Pain Med 2001;26:545–50.
17. Gambling DR, Sharma SK, Ramin SM, et al. A randomized study of combined spinal epidural analgesia versus intravenous meperidine during labor. Anesthesiology 1998;89:1336–44.
18. Freeman RK. Problems with intrapartum fetal heart rate monitoring interpretation and patient management. Obstet Gynecol 2002;100:813–26.
19. Tacker SB, Stroup D, Chang M. Continuous electronic heart rate monitoring for fetal assessment during labor (Cochrane review). Cochrane Library 2002:4.
20. Van de Velde M, Pexsters A, Honnens M. Fetal assessment: do newer technologies offer better assessment and outcome? Curr Opin Anaesthesiol 2003;16:253–6.
21. Liston R, Crane J, Hamilton E, et al. Fetal health surveillance in labour. J Obstet Gynaecol Can 2002;24:250–76.
22. Dunn SM, Connelly NR, Steinberg RB, et al. Intrathecal sufentanil versus epidural lidocaine and epinephrine and sufentanil for early labor analgesia. Anesth Analg 1998;87:331–5.
23. Campbell DC, Camann WR, Datta S. The addition of bupivacaine to intrathecal sufentanil for labor analgesia. Anesth Analg 1995;81:305–9.
24. Blumgart CH, Ryall D, Dennison B, Thompson-Hill LM. Mechanism of extension of spinal anaesthesia by extradural injection of local anesthetic. Br J Anaesth 1992;69:457–60.
25. Stienstra R, Dahan A, Alhadi ZRB. Mechanism of action of an epidural top-up in combined spinal epidural anesthesia. Anesth Analg 1996;83:382–6.
26. Stienstra R, Dilrosun-Alhadi BZ, Dahan A, et al. The epidural top-up in combined spinal epidural anesthesia: the effect of volume versus dose. Anesth Analg 1999;88:810–4.
27. Van de Velde M, Teunkens A, Hanssens M, et al. Postdural puncture headache following combined spinal epidural or epidural anesthesia in obstetric patients. Anesth Intensive Care 2001;29:595–9.