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Epidural Sufentanil and Bupivacaine for Labor Analgesia and Doppler Velocimetry of the Umbilical and Uterine Arteries

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Background: **The pain of parturition is associated with major physiologic alterations mediated by neurohumoral factors and increased activation of the sympathetic nervous system. Epidural local anesthetics abolish or alleviate many of the pain-mediated responses by reducing maternal catecholamine levels, inducing sympathectomy and consequent vasodilatation. The hormone response to surgical stress is not attenuated after epidural opioids as efficiently as after local anesthetics. Opioid receptors may modulate sympathetic outflow at a spinal level. This study was performed to compare the effects of epidural sufentanil and bupivacaine on the uterine and placental circulation.**

Methods: **Utilizing a prospective randomized, double-blind study design, 30 healthy women at term were examined employing a color Doppler technique to assess and compare the effects of analgesia using sufentanil or bupivacaine epidurally during the first stage of labor on blood flow velocity waveforms in the uterine and umbilical arteries.**

Results: **Effective analgesia was provided by both drugs, bupivacaine and sufentanil. Uterine and umbilical blood velocity waveform indices did not change significantly. There was, however, a significantly greater incidence of fetuses with changes in heart rate tracings in the sufentanil group, decreased variability being the most frequent. Maternal side effects attributable to sufentanil were common but mild. No patient became hypotensive in either group.**

Conclusions: **Epidural sufentanil and bupivacaine provide effective analgesia with acceptable side effects during the first stage of labor in healthy parturients. Neither drug had any detrimental effects on blood flow indexes reflecting peripheral vascular resistance in the umbilical and uterine arteries in healthy parturients. (Key words: Analgesia: obstetric. Analgesics, epidural: sufentanil. Anesthetic techniques: epidural. Anesthetics, local: bupivacaine. Measurement technique: Doppler ultrasound. Monitoring: fetal heart rate. Placenta: blood flow velocity. Uterus: blood flow.)**

MATERNAL psychologic stress and pain during labor evoke diverse physiologic changes mediated by neurohumoral factors and increased activation of the autonomic nervous system.[1] Consequently, maternal circulating catecholamine levels are higher during labor than during the last trimester of pregnancy.[2] This response may be deleterious to the fetus as reflected by the observation that elevated plasma norepinephrine levels produced by stress are associated with a significant decrease in uterine blood flow in the pregnant ewe.[3] Many such pain-mediated responses can be alleviated with regional anesthesia. After properly administered epidural blockade with local anesthetics, placental blood flow increases during normal labor[4] and in preeclampsia,[5] probably due to reduced maternal circulating catecholamine levels.[6] Sympathectomy and the consequent decrease in uterine vascular resistance related to epidural analgesia may have a salutary effect on the placental perfusion as well, since the more widespread sympathectomy obtained with larger volumes of epidural local anesthetics causes a better improvement in placental circulation[4,5] than does a smaller segmental block.[7,8]

Epidural opioid administration can provide rapid, long-lasting pain relief,[9] and opioids, especially in combination with local anesthetics, have become widely used for labor analgesia. The effect of epidural opioids on the body's response to stress, however, is less marked than that of local anesthetics despite similar analgesia.[10] Thus pain relief itself does not necessarily suppress the increase in stress hormones. Theoretically, epidural opioids for obstetric analgesia are an attractive option because autonomic function and, consequently, maternal cardiovascular parameters are better pre-

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served. Clinical findings do not support this speculation, however, since there seems not to exist any significant difference in the incidence of maternal hypotension between parturients receiving an opioid drug and a local anesthetic epidurally.[11,12] The lack of significance may be due to the small number of patients studied, but in any case, the use of epidural opioids for labor analgesia may not be free of the risk of hypotension.

Anatomic and neurophysiologic studies suggest that there may be a functional relation between opioids and the sympathetic nervous system at a spinal level. There is a dense binding of opioid ligands on the preganglionic sympathetic neurons of the thoracolumbar spinal cord in the rat,[13] and bradycardia and decreased blood pressure occur after an intrathecal injection of μ-receptor agonist.[14] Cardiovascular functions may be regulated by spinal opioids in humans as well.[15]

The effects of epidural opioids on the maternal and fetal circulation have been studied previously in animals,[16,17] but not in human pregnancies. We report here on work carried out to investigate and compare the effects of two drugs, bupivacaine and sufentanil, administered epidurally in a randomized, double-blind fashion on maternal uterine and fetal umbilical artery blood flow dynamics during normal labor using a modern color Doppler technique.

Materials and Methods

The research design was approved by the Ethics Committee of the University of Oulu. Healthy women with uncomplicated singleton pregnancies at term were invited to participate if they requested epidural analgesia. All of the patients were in active first-stage labor with cervical dilatation 3–5 cm upon enrollment. The aim of the research was explained, and informed verbal consent was obtained. The parturient was then randomly allocated to one of the two analgesic groups. Written consent was obtained once the patient was pain-free.

The anesthetic procedures were performed according to the same protocol by one of the authors (S. A.). The epidural space was identified in the L1–L2 or L2–L3 interspace with the patient in the lateral position, and a catheter was inserted 2–3 cm into it. After the patient had resumed a semirecumbent position, the analgesic solution was injected in two doses of 6 ml, with a 5-min interval between. The choice of agent was made by blindly picking a paper with the name of the solution written on it from an envelope. The solution contained either 12 ml 0.25% bupivacaine (30 mg) or 50 μg sufentanil diluted in normal saline to a total volume of 12 ml. The solutions were prepared by a recovery room nurse not involved in the study. If analgesia was not adequate after 12 ml of the drug, 3 ml 0.25% bupivacaine was administered. The patient was excluded if the additional dose failed to have any effect or if the patient was found afterward to have been in the sufentanil group. Five hundred milliliters of balanced electrolyte solution was given intravenously during the establishment of the labor analgesia. Maternal arterial pressure was recorded at 5-min intervals using an automated noninvasive device. Maternal hypotension, defined as a systolic arterial pressure of less than 100 mmHg, was treated by increasing the infusion and, if this was ineffective, by intravenous ephedrine.

The ultrasound Doppler measurements were obtained before the induction of epidural anesthesia and after the patient reported analgesia to be satisfactory. The interval from the last drug injection to the beginning of the second Doppler recording was 16.8 min (range 9–40 min) in the bupivacaine group and 23.9 min (range 13–43 min) in the sufentanil group. All the recordings were made by the same obstetrician (J. R.) during fetal apnea between the uterine contractions with the parturient in a left semirecumbent position. Both maternal uterine arteries (main branch on the placental and nonplacental side of the uterus) and the fetal umbilical artery were identified by a color Doppler technique (Toshiba, model SSH-140A), and their blood velocity waveforms were recorded by the pulsed Doppler method (3.75-MHz sector probe). Three consecutive, correctly imaged waveforms were examined from each recording, and a mean value was derived for the pulsatility index, defined as the difference between the peak systolic and end-diastolic values divided by the averaged maximum flow velocity of the cycle. The fetal heart rate (FHR) was derived from the umbilical Doppler signal. An attempt was made to examine the same sites on the umbilical and uterine arteries for each insonation period. Maternal arterial pressure was recorded at 2-min intervals during the second ultrasound measurement.

The patients' pain was evaluated using a 10-cm visual analog scale before the block and immediately after the second ultrasound measurement. Fetal heart rate was monitored continuously *via* a scalp electrode after spontaneous rupture of the membranes or indicated amniotomy, and uterine activity by external tocodyn-

Table 1. Patient Data

	Bupivacaine Group (n = 15)	Sufentanil Group (n = 15)
No. nulliparous	12	15
Age* (yr)	26.5 ± 5.3	27.1 ± 3.9
Weight* (kg)	74.2 ± 12.9	73.2 ± 13.0
Height*	165.9 ± 4.9	164 ± 6.9
Median pain score		
Before analgesia	8.5	9.0
After analgesia	0	0

* Values are mean ± SD.

amometry. The FHR tracings were analyzed visually at the end of the trial by an obstetrician (P. J.), who was unaware of the drug used. Three characteristics were identified for each tracing: baseline FHR, FHR variability, and periodic excursions of the FHR (accelerations and decelerations). The visual criterion for normal variability in FHR tracings was >5 beats/min. Fetal heart rate parameters were assigned for the 20 min before the epidural blockade, and changes recorded during the 60 min after the first dose of the drug. After the measurements had been completed, management of the labor and delivery proceeded according to the hospital's standard regimens.

Statistical comparisons between the groups were performed by means of two-sample *t* tests, and those within the groups by the *t* test for paired data. Fetal heart rate parameters were compared using Fisher's exact probability test. A *P* value less than .05 was considered significant.

Results

Thirty-one parturients participated in the trial, including one patient who received sufentanil, was given an additional dose of bupivacaine because of inadequate analgesia, and therefore was excluded from the eventual series. The remaining 30 patients were divided equally between the groups (table 1). The scores for pain initially and immediately after the second Doppler recording were comparable between the groups. All the patients in both groups ranked the analgesia as excellent, but two in the bupivacaine group required 15 ml of local anesthetic. Even though mean maternal arterial blood pressures were significantly less in both groups during the establishment of epidural anesthesia and during the second ultrasound recording as compared with values before epidural analgesia, none of the patients became hypotensive or needed a vasopressor (table 2). Eight patients of 15 experienced side effects after sufentanil. Pruritus (6 patients) and sedation (2 patients) were mild, and none of the patients requested treatment. Four patients became dizzy, and one of them vomited. No side effects were noted after bupivacaine administration.

None of the fetuses showed FHR evidence of fetal distress prior to epidural analgesia. Changes in FHR parameters were observed in 2 of 13 in the bupivacaine group and in 8 of 12 in the sufentanil group ($P < .02$). The most frequent finding was decreased FHR variability, one case in patients receiving bupivacaine and seven in those receiving sufentanil. Early decelerations were noted in one patient in the bupivacaine group and two in the sufentanil group. The mean FHR remained stable throughout the period. Mean maternal

Table 2. Maternal Hemodynamics before Epidural Analgesia, during Its Induction, and during the Second Ultrasound Measurement

	Before Epidural Analgesia	During Epidural Analgesia Induction	*P*	During Second Ultrasound Measurement	*P*
Bupivacaine group					
Systolic arterial pressure (mmHg)	133.1 ± 16.1	125.0 ± 18.4	<.001	120.0 ± 14.5	<.001
Diastolic arterial pressure (mmHg)	75.6 ± 14.7	72.7 ± 16.3	.200	70.2 ± 13.2	.089
Heart rate (beats/min)	85.5 ± 12.0	85.7 ± 11.5	.858	88.4 ± 15.0	.586
Sufentanil group					
Systolic arterial pressure (mmHg)	130.6 ± 11.0	124.4 ± 7.7	.003	122.5 ± 10.0	.019
Diastolic arterial pressure (mmHg)	80.5 ± 11.2	71.9 ± 7.4	.050	71.8 ± 6.9	.014
Heart rate (beats/min)	75.8 ± 9.9	75.3 ± 9.4	.687	74.4 ± 9.3	.530

Values are expressed as mean ± SD.

P values indicate the significances of the differences from the baseline measurements.

uterine pulsatility index values did not change significantly at any time on either the placental or the nonplacental side in either group, and there were no differences between the groups. There was no significant change in the mean pulsatility index for the fetal umbilical artery relative to baseline values in either group or between the groups (table 3).

No interventions due to the fetal distress were necessary during the later stages of labor. The mean birth weights of the neonates were 3,798 ± 485 g and 3,660 ± 393 g in the bupivacaine and sufentanil groups, respectively. One patient in each group underwent a cesarean section, and two in the sufentanil group were delivered by vacuum extraction. All the newborn infants had Apgar scores of 8 or higher at 5 min, except for one in the sufentanil group with score of 7. Later neonatal courses were uneventful in every case.

Discussion

The Doppler ultrasound technique allows noninvasive, reproducible evaluation of blood flow in the uterine and umbilical arteries.[18] Due to a source of cumulative errors in the estimation of blood flow volume, the main approach tends to be analysis of various indexes derived from the blood flow velocity waveforms. Pathologically high index values in the uterine and umbilical arteries have been found to serve as sensitive early warning signals with a high positive predictive value for fetal distress.[19] Indexes, such as pulsatility index, are related to the vascular resistance distal to the point of measurement, provided that the upstream hemodynamic changes remain relatively minor.[20] These upstream circulatory factors include cardiac contractility, heart rate, and blood viscosity. The indexes also are affected by the site of measurement. The pulsed wave Doppler technique combined with real-time ultrasound facilities makes discrimination of the measurement site possible. A recent application of Doppler ultrasound is color flow mapping, in which the directions and velocity of blood flow are coded in color and superimposed on a real-time image. Color systems allow accurate identification of small, short vessels, which is valuable especially for the location and assessment of uteroplacental circulation.

The greatest benefit from epidural opioids in labor analgesia has been achieved by combining them with local anesthetics.[11] An opioid alone was used in the present series, however, since our aim was to evaluate the circulatory effects of an analgesic agent during labor mainly with respect to pain transmission. To avoid responses related to pain itself, the epidural opioid would have to provide especially effective analgesia. For these reasons, sufentanil, a potent lipid-soluble opioid with a rapid onset of action,[21] was chosen. The dose of 50 μg is that reported by Steinberg and coworkers to produce the lowest pain scores.[22] Two recent reports from the same authors document the safety of 50 μg sufen-

Table 3. Mean Values for Doppler Velocimetric Variables

	Bupivacaine Group (n = 15)	Sufentanil Group (n = 15)	*P*
Fetal heart rate (beats/min)			
Before epidural	140.3 ± 10.1	135.5 ± 10.7	.216
After epidural	136.3 ± 9.6	133.6 ± 10.1	.455
Significance of difference (*P*)	0.162	.475	
Uterine artery PI nonplacental side			
Before epidural	0.76 ± 0.28	0.78 ± 0.18	.759
After epidural	0.73 ± 0.19	0.81 ± 0.23	.321
Significance of difference (*P*)	0.697	.731	
Uterine artery PI placental side			
Before epidural	0.65 ± 0.19	0.67 ± 0.14	.861
After epidural	0.64 ± 0.15	0.75 ± 0.17	.076
Significance of difference (*P*)	0.710	0.200	.076
Umbilical artery PI			
Before epidural	0.80 ± 0.22	0.78 ± 0.13	.242
After epidural	0.77 ± 0.10	0.82 ± 0.14	.202
Significance of difference (*P*)	0.550	0.163	

Values are mean ± SD.

PI = pulsatility index.

tanil.[23,24] The dose was given epidurally with local anesthetics for cesarean section analgesia before delivery, and no adverse neonatal effects were found upon neurobehavioral assessment. In the current series, epidural sufentanil for labor analgesia did not significantly affect umbilical and placental or nonplacental uterine artery blood flow velocity indexes in cases of uncomplicated pregnancy when maternal arterial pressure remained stable. The finding is similar to those of Craft and coworkers, who administered 50 and 100 μg fentanyl into the epidural space of chronically instrumented, nonstressed pregnant sheep and observed no significant changes in uterine artery blood flow.[17] The same authors previously had found a gradual decrease in uterine blood flow that reached statistical significance 120 min after the epidural injection of 5 mg morphine.[16] Both sets of results showed a tendency for maternal bradycardia. We are unaware of any research on pregnant women in which the maternal or fetal circulatory effects of the epidural administration of opioids have been evaluated. Beavis *et al.* gave epidural fentanyl preoperatively to nonpregnant patients undergoing thoracotomy and found no significant changes in cardiac output or hepatic blood flow.[25] Lindblad *et al.* recorded a decrease in fetal aortic volume blood flow after intramuscular meperidine, while it increased after epidural labor analgesia with bupivacaine in a manner similar to that during labor without analgesia.[26]

Fetal hear rate variability decreased in more than half of the fetuses after sufentanil administration. We believe that this was a direct drug effect on the central nervous system of the fetus as there were no significant changes in the indexes reflecting peripheral vascular resistance in the umbilical artery or uterine arteries nor any maternal hypotension at the time of the FHR changes. It has been demonstrated previously that intravenous administration of 50–100 μg fentanyl results in reduced FHR variability in half of the cases.[27] A recent paper reports no changes in FHR variability after 75 μg fentanyl administered epidurally during labor[28] and a reduction in variability only after epidural lidocaine, which was given to all the patients for labor analgesia before opioid administration.

We found no significant changes in any of the blood flow velocity waveform indexes measured in patients receiving epidural bupivacaine. Several authors have approached this topic previously in trials that were neither blinded nor randomized[29–32]; they all used bupivacaine in larger doses than we did and with variable anesthetic techniques. Even so, none found any significant changes in the Doppler velocimetric indexes of the uterine and umbilical arteries after epidural analgesia with a local anesthetic during labor. These experiences suggest that properly conducted epidural analgesia during labor in normal gravidas does not seem to affect uterine or umbilical vascular resistance. In one investigation,[32] maternal cardiac function and uteroplacental circulation were assessed simultaneously. There was no significant change in mean maternal cardiac output after epidural anesthesia with a local anesthetic.

We conclude that epidural bupivacaine and sufentanil for pain relief during the first stage of labor as used here were equally effective and had no detrimental effects on blood flow waveform indexes for the umbilical or uterine vasculature. Side effects were common after epidural sufentanil, but they were mostly mild and did not require treatment. Despite the reductions in FHR variability, we observed no clinical signs of fetal distress. However, as a similar pattern may be indicative of fetal hypoxemia and acidosis, the use of 50 μg sufentanil epidurally may lead to unnecessary obstetric interventions, whereas in cases of a compromised fetus, the sufentanil-related decrease in FHR variability may mask ensuing fetal distress. Even so, as epidural sufentanil can provide adequate analgesia for labor without adverse vascular effects in the uterine and umbilicoplacental circulation, it could provide an alternative when attempting to avoid the unwanted effects of epidural local anesthetics.

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