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Cesarean Delivery

A Randomized Trial of Epidural Analgesia versus *Intravenous Meperidine Analgesia during Labor in Nulliparous Women*

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Background: **Controversy concerning increased cesarean births as a result of epidural analgesia for relief of labor pain has been attributed, in large part, to difficulties interpreting published studies because of design flaws. In this study, the authors compared epidural analgesia to intravenous meperidine analgesia using patient-controlled devices during labor to evaluate the effects of labor epidural analgesia, primarily on the rate of cesarean deliveries while minimizing limitations attributable to study design.**

Methods: **Four hundred fifty-nine nulliparous women in spontaneous labor at term were randomly assigned to receive either epidural analgesia or intravenous meperidine analgesia. Epidural analgesia was initiated with 0.25% bupivacaine and was maintained with 0.0625% bupivacaine and fentanyl 2 μg/ml at 6 ml/h with 5-ml bolus doses every 15 min as needed using a patient-controlled pump. Women in the intravenous analgesia group received 50 mg meperidine with 25 mg promethazine hydrochloride as an initial bolus, followed by 15 mg meperidine every 10 min as needed, using a patient-controlled pump. A written procedural manual that prescribed the intrapartum obstetric management was followed for each woman randomized in the study.**

Results: **A total of 226 women were randomized to receive epidural analgesia, and 233 women were randomized to receive intravenous meperidine analgesia. Protocol violations occurred in 8% (38 of 459) of women. There was no difference in the rate of cesarean deliveries between the two analgesia groups (epidural analgesia, 7% [16 of 226; 95% confidence interval, 4–11%] *vs.* intravenous meperidine analgesia, 9% [20 of 233; 95% confidence interval, 5–13%]; $P = 0.61$). Significantly more women randomized to epidural analgesia had forceps deliveries compared with those randomized to meperidine analgesia (12% [26 of 226] *vs.* 3% [7 of 233]; $P < 0.001$). Women who received epidural analgesia reported lower pain scores during labor and delivery compared with women who received intravenous meperidine analgesia.**

Conclusions: **Epidural analgesia compared with intravenous meperidine analgesia during labor does not increase cesarean deliveries in nulliparous women.**

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THE use of epidural analgesia during labor has greatly increased in the United States, from 22% of births in 1981 to 66% in 1997,[1] coincident with the significant escalation in the cesarean delivery rate.[2] The coincidence of increasing cesarean delivery and labor epidural analgesia rates has prompted controversy as to whether the use of epidural analgesia is causally associated with an increased risk of cesarean delivery. Indeed, in a recent evaluation of cesarean delivery sponsored by the American College of Obstetricians and Gynecologists,[3] it was concluded that "there was considerable evidence suggesting that there is in fact an association between the use of epidural analgesia for pain relief during labor and the risk of cesarean delivery." Although it has been acknowledged that all women in labor should have access to effective pain relief,[4,5] the possible trade-off between superior pain relief with epidural analgesia during labor and the alleged risk of cesarean delivery has been a cause of considerable concern to expectant parents, obstetricians, and anesthesiologists.

The controversy about the relation of epidural analgesia during labor and cesarean delivery has been attributed, in large part, to difficulties interpreting published studies because of flaws in design.[3] Major design problems have included retrospective analyses rather than randomized trials,[6–8] small sample size,[9] inclusion of both parous and nulliparous women with markedly differing risks of cesarean delivery as a result of dystocia,[10,11] crossover of women from the control arm to epidural analgesia because of inadequate pain relief,[10,12,13] and concern about the ability to generalize studies that have shown no epidural-related increase in cesarean rates in populations with preexisting low rates of cesarean delivery.[3]

We performed this randomized study to compare epidural analgesia during labor to intravenous meperidine analgesia during labor. Our primary purpose was to evaluate the effects of epidural analgesia during labor on the rate of cesarean deliveries while minimizing the aforementioned concerns about study design. We limited our trial exclusively to nulliparous women with uncomplicated pregnancies admitted in spontaneous labor at term, and all women enrolled self-controlled their analgesia using bedside pump devices. Patient-controlled

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analgesia in the control arm has previously been shown to minimize crossovers.[11]

Methods

The study protocol was developed by investigators from the Departments of Anesthesiology and Obstetrics and Gynecology and approved by the institutional review board of the University of Texas Southwestern Medical Center (Dallas, Texas). The study commenced on October 1, 1998, and ended on November 3, 2000. Healthy nulliparous parturients with a singleton cephalic gestation at term and in spontaneous labor were offered participation in this randomized investigation. Women giving written consent were randomly assigned using numbered sealed envelops to receive either epidural analgesia or intravenous meperidine analgesia at their first request for labor analgesia. The randomization sequence was computer derived in blocks of 20 subjects.

Obstetric Management

All pregnancies were managed by certified nurse–midwives under direct supervision by obstetric faculty and house officers following a written protocol established by the medical staff. Routine intrapartum management of all women included intravenous fluid administration and continuous electronic fetal heart rate surveillance for 30 min after commencing epidural or intravenous analgesia. Continuous internal electronic fetal heart rate monitoring was used in women with meconium-stained amnionic fluid, auscultated fetal heart rate decelerations, or inadequate progress of labor. Pelvic examinations were performed approximately every 2 h to evaluate the progress of labor.

Cervical change of less than 1 cm/h coincidental with hypotonic uterine contractions measured using intrauterine pressure transducers resulted in oxytocin augmentation of labor. Oxytocin was administered per written protocol, which has been described previously.[14] Briefly, oxytocin starting at 6 mU/min was increased by 6 mU/min at 40-min intervals up to a maximum of 42 mU/min. Uterine activity of 200–250 Montevideo units for 2–4 h was considered adequate. Dystocia was diagnosed when adequate uterine activity did not result in progressive cervical dilation or descent of the fetal head. Indications for the use of forceps were limited to inadequate voluntary pushing or fetal heart rate abnormalities. Inadequate voluntary pushing was determined at the bedside, and if good descent was observed when effort was made (and, conversely, if no descent was observed when little effort was made), then lack of descent caused by inadequate maternal expulsive efforts was diagnosed. Umbilical artery blood for analysis of gases was obtained at all births from a doubly clamped cord segment.

Labor Analgesia

Epidural Analgesia. Women randomized to epidural analgesia received an intravenous bolus dose of 500 ml Ringer lactate, after which analgesia was initiated using an indwelling catheter inserted into the lumbar epidural space *via* a 17-gauge Tuohy needle. Analgesia was achieved with 3-ml increments of 0.25% bupivacaine to a bilateral T-10 sensory level after a negative test dose of 3 ml of 1% lidocaine with epinephrine. Epidural analgesia was maintained with 0.0625% bupivacaine and 2 μg/ml fentanyl at 6 ml/h with 5-ml bolus doses every 15 min as needed using a patient-controlled analgesia pump (Abbott Pain Manager APM II; Abbott Laboratories, North Chicago, IL). This was maintained throughout the first stage of labor. If progress during the second stage of labor was inadequate after 1 h, the infusion was halved or discontinued to restore maternal expulsive efforts. Additional bolus doses of fentanyl or bupivacaine were injected to overcome inadequate analgesia. If adequate pain relief could not be provided despite additional bolus doses of fentanyl or bupivacaine, the epidural catheter was replaced. Left uterine displacement was maintained to avoid aortocaval compression.

Maternal blood pressure was recorded every 5 min for 30 min and then every 30 min until delivery. Intravenous fluids were given to treat hypotension, defined as a systolic blood pressure less than 25% of the baseline or a systolic blood pressure less than 100 mmHg. Persistent hypotension was treated with 5 mg ephedrine administered intravenously as needed.

Intravenous Meperidine Analgesia. Women randomized to parenteral analgesia received 50 mg meperidine with 25 mg promethazine hydrochloride administered intravenously as an initial bolus dose, after which a patient-controlled-pump (Abbott-Lifecare 4100; Abbott Laboratories) was set up to deliver 15 mg meperidine every 10 min as needed until delivery. Additional 25-mg doses of meperidine were given on request, not to exceed 100 mg in 2 h. Epidural analgesia was administered when the patient deemed her pain relief unacceptable. Maternal blood pressure was recorded as previously described in women who received epidural analgesia.

Pain was assessed with a linear 10-cm visual analog scale (0 = no pain, 10 = worst possible pain) before the initiation of analgesia and during the first stage (8–10-cm cervical dilatation) and second stage (after 10-cm cervical dilatation with maternal pushing efforts) of labor. In addition, the quality of pain relief during the first and second stage of labor was reassessed within 24 h after delivery using a four-point descriptive scale of excellent, good, fair, or poor.

Statistical Analysis

All tests of significance were performed using two-tailed tests. Data were analyzed using SAS statistical software (SAS Institute, Inc., Cary, NC). Statistical signifi-

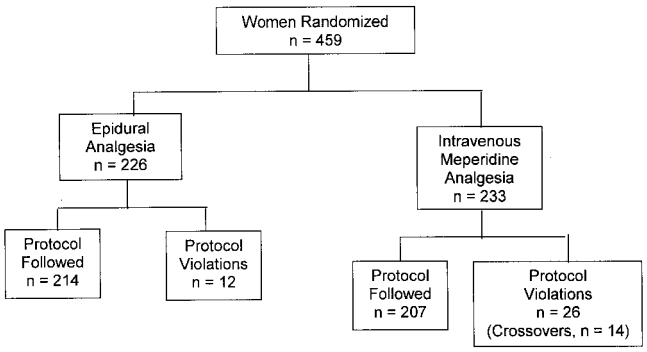

Fig. 1. Distribution of women randomized to epidural analgesia or intravenous meperidine analgesia. Protocol violations include women who refused their allocated analgesia or those who crossed over to the other analgesia study group because of inadequate pain relief.

cance ($P < 0.05$) was determined using unpaired Student *t* test, Pearson chi-square test, and Mann–Whitney U test as indicated. Data were analyzed according to group assignment at randomization regardless of the eventual analgesia received. Secondarily, patients compliant to their randomization assignment were also compared.

We estimated that 446 total subjects would need to be randomized based on a projected cesarean delivery rate of 4% in the intravenous meperidine analgesia group[10] and assuming an 6% absolute increase in cesarean delivery rate as a result of epidural analgesia giving a 10% cesarean delivery rate. This sample size was calculated using a one-sided 0.05 probability of type I error and 80% power. The use of one-tailed test was only for the purpose of *a priori* power analysis to estimate the minimum number needed to demonstrate a difference.

Results

A total of 459 women were randomized in this investigation. Protocol violations occurred in 38 women (8%; fig. 1). Of these 38 women, 14 who received intravenous meperidine as randomized crossed over to epidural analgesia because of inadequate pain relief, and 24 women refused their allocated analgesia and received other analgesia. As shown in table 1, there were no significant differences in maternal demographic characteristics between the two study groups. Results of pelvic examinations at the time of analgesia for labor pain are shown in table 2. There were no significant differences between the study groups with respect to cervical dilation, effacement, or station of the fetal head.

Labor events were analyzed in relation to the type of analgesia used, and the results are shown in table 3. Epidural analgesia was significantly associated with prolongation of the first ($P = 0.03$) and second ($P = 0.008$) stages of labor, need for augmentation of labor with oxytocin ($P = 0.01$), maternal fever (temperature $\geq$ 38°C, $P < 0.001$), and hypotension ($P = 0.001$). The type of analgesia was not significantly related to fetal heart rate abnormalities after analgesia had commenced.

Table 1. Maternal Demographic Characteristics in Women Randomized to Epidural Analgesia Compared with Intravenous Meperidine Analgesia

Characteristic	Epidural Analgesia (n = 226)	Intravenous Meperidine Analgesia (n = 233)	*P* Value
Age (yr)	21 ± 4	21 ± 4	0.69
Height (cm)	174 ± 8	171 ± 8	0.06
Weight (kg)	72 ± 12	73 ± 14	0.26
Gestational age (weeks)	39.3 ± 1.3	39.2 ± 1.4	0.82
Race			0.91
Hispanic	184 (79)	175 (77)	
African-American	39 (17)	40 (18)	
White	10 (4)	11 (5)	

Data are presented as N (%) or mean ± SD.

The methods of delivery based on intention-to-treat analysis are shown in table 4. Significantly fewer women randomized to epidural analgesia experienced spontaneous deliveries compared with those randomized to intravenous meperidine analgesia ($P = 0.04$). This difference was a result of significantly increased forceps deliveries (both low and outlet forceps) rather than cesarean deliveries. Specifically, 12% of women receiving epidural analgesia had forceps deliveries compared with 3% in the parenteral analgesia group ($P < 0.001$). The overall cesarean rates for epidural analgesia and intravenous meperidine analgesia were 7% (95% confidence interval, 4–11%) and 9% (95% confidence interval, 5–13%), respectively ($P = 0.61$). There were no significant differences in cesarean delivery for dystocia or fetal heart rate abnormalities.

Infant outcomes are summarized in table 5. There were no neonatal deaths. Mean birth weight as well as the incidence of macrosomic infants ($\geq$ 4,000 g) were not significantly different between the two analgesia study groups. One-minute Apgar scores were significantly lower in the intravenous meperidine analgesia group, but there was no significant difference in the 5-min scores. Significantly more neonates required naloxone for depressed respiration with intravenous meperidine analgesia than with epidural analgesia (6 *vs.* 0%; $P < 0.001$). Umbilical artery blood acidemia was not

Table 2. Results of Pelvic Examination at the Time of Analgesia for Labor Pain

Pelvic Examination	Epidural Analgesia (n = 226)	Intravenous Meperidine Analgesia (n = 233)	*P* Value
Cervical dilation (cm)	4 (4, 5)	4 (4, 5)	0.7
Effacement of cervix (%)	90 (80, 100)	90 (80, 100)	0.3
Fetal head station (cm)	−1 (−1, 0)	−1 (−1, 0)	0.33

Data are presented as median (first quartile, third quartile).

Table 3. Labor Events in Women Randomized to Epidural Analgesia Compared with Intravenous Meperidine Analgesia

Labor Event	Epidural Analgesia (n = 226)	Intravenous Meperidine Analgesia (n = 233)	*P* Value
Interval from initiation of analgesia to complete cervical dilatation (min)	302 ± 189	261 ± 188	0.03
Second stage of labor (min)	56 ± 42	45 ± 42	0.008
Oxytocin augmentation after initiation of analgesia	102 (45)	78 (34)	0.01
Fever ≥ 38°C	75 (33)	16 (7)	< 0.001
Hypotension after analgesia	13 (6)	1 (0.4)	0.001
FHR abnormalities with 30 min after initiation of analgesia	15 (7)	12 (5)	0.56

Data are presented as mean ± SD or N (%).

FHR = fetal heart rate decelerations to less than 90 beats/min, late deceleration.

related to the type of analgesia given the mother. Abnormal carbon dioxide tension (≥ 65 mmHg) was significantly more common in the meperidine analgesia group ($P = 0.019$). Two neonates in the epidural analgesia group and one in the intravenous meperidine analgesia group required transfer to the neonatal intensive care unit.

Because 8% of the randomized patients did not comply with the analgesia protocol (fig. 1), we separately compared patients who did comply with their allocated analgesia protocol. There were no significant differences in demographic characteristics and pelvic examinations at the time of analgesia between the protocol-compliant groups. Analysis of the protocol-compliant groups also showed no significant difference between the epidural analgesia and intravenous meperidine analgesia groups in the rate of cesarean deliveries (epidural analgesia, 7% [15 of 214; 95% confidence interval, 4–11.3%] *vs.* parenteral analgesia, 8% [16 of 207; 95% confidence interval, 4.4–12.2%]; $P = 0.85$). However, epidural analgesia was associated with a higher forceps delivery rate (epidural analgesia, 12% [26 of 214] *vs.* intravenous meperidine analgesia, 2.4% [5 of 207]; $P < 0.001$), prolonged first and second stages of labor, increased incidence of oxytocin augmentation, maternal fever, and hypotension.

Table 4. Method of Delivery in Women Randomized to Epidural Analgesia or Intravenous Meperidine Analgesia

Method of Delivery	Epidural Analgesia (n = 226)	Intravenous Meperidine (n = 233)	*P* Value
Spontaneous	184 (81)	206 (88)	0.04
Forceps			
Total	26 (12)	7 (3)	< 0.001
Low	15 (7)	5 (2)	0.02
Outlet	11 (5)	2 (1)	0.01
Cesarean delivery			
Total	16 (7)	20 (9)	0.61
Dystocia	13 (6)	17 (7)	0.57
Nonreassuring FHR	3 (1.3)	3 (1.3)	1

Data are presented as N (%). Low forceps are defined as application at +2 to +4 cm below the ischial spines. Outlet forceps are defined as application when the fetal head is on the perineum.

FHR = fetal heart rate.

The preanalgesic visual analog pain scale scores were similar between the two study groups (epidural, 9 ± 1.6 *vs.* intravenous meperidine, 9 ± 1.7; $P = 0.74$). Women who received epidural analgesia reported lower pain scores during the first (epidural, 2 ± 3 *vs.* meperidine, 5 ± 3; $P < 0.01$) and second stages (epidural, 3 ± 3 *vs.* meperidine, 5 ± 4; $P < 0.01$) of labor. When parturients were queried within 24 h of delivery, 95% of women who received epidural analgesia rated their satisfaction as excellent or good compared with 69% of women who received intravenous meperidine analgesia ($P < 0.001$).

Discussion

The primary finding in this investigation was that cesarean deliveries were not increased as a result of epidural analgesia during labor in nulliparous women. This was true for the overall cesarean rate as well as cesareans for dystocia or nonreassuring fetal heart rate. Moreover, epidural analgesia provided effective pain relief during labor and delivery and had no significant adverse effects on infant outcome.

Table 5. Infant Outcomes According to the Type of Analgesia Used for Relief of Labor Pain

Infant Outcome	Epidural Analgesia (n = 226)	Intravenous Meperidine Analgesia (n = 233)	*P* Value
Birth weight (g)	3,311 ± 394	3,288 ± 389	0.55
≥ 4,000 g	10 (4)	10 (4)	1.0
Apgar scores			
< 7 at 1 min	9 (4)	33 (14)	< 0.001
< 7 at 5 min	1 (0.4)	4 (2)	0.37
Naloxone*	0	13 (6)	< 0.001
Intensive care admission	2 infants	1 infant	—
Umbilical artery blood pH			
≤ 7.10	6 (3)	14 (7)	0.1
≤ 6.99	1 (0.5)	3 (1.4)	0.62
Umbilical blood P_{CO_2}			
≥ 65 mmHg	30 (15)	51 (24)	0.019

Data are presented as mean ± SD or N (%).

* Naloxone administered to reverse respiratory depression at birth.

P_{CO_2} = partial pressure of carbon dioxide.

Several retrospective studies[6–8] and prospective studies conducted over the past decade[15] have attempted to evaluate the effect of epidural analgesia during labor on cesarean delivery. Retrospective studies suffer from selection bias because women selecting epidural analgesia may have more intense pain as a result of more difficult labor, and hence are intrinsically at greater risk for dystocia necessitating cesarean delivery.[16–18] Prospective studies have also suffered from methodologic limitations.[19] Many women have firm views on the type of analgesia they prefer in labor and are reluctant to consent to receiving a predetermined method of analgesia, or they may consent and then withdraw from the study, thereby contributing to protocol failures.[10,11] Another important consideration is unsatisfactory pain relief in women randomized to the control group, which ethically mandates permitting these women to cross over to epidural analgesia.[10,12,13] This, in turn, significantly distorts both study arms. Methodologic problems such as these have prevented definitive conclusions from several prospective trials as to whether labor epidural analgesia causes cesarean births. In this well-controlled randomized trial, protocol failure was only 8%, and the analgesic technique in the control arm, which allowed women to control their own pain relief, minimized crossovers to 6%. We are of the view that these results permit us to compare the effects of epidural analgesia on labor with as little confounding as is pragmatically possible.

It might be argued that our overall primary cesarean rate of 8% with epidural analgesia during labor is low and precludes the ability to generalize our results. Although an 8% primary cesarean rate seems low when compared with 17.9% (range by state, 11.5–24.3%), the overall primary rate in United States in 1996 for nulliparous women,[20] we emphasize that the population selected for our trial represents only a portion of this national primary rate, *i.e.*, we included only nulliparous women presenting in spontaneous active labor without complications such as hypertension and with singleton presentations between 36 and 41 weeks' gestation. This group accounts for 30% of nulliparous women delivered at our hospital. The question then becomes, what is the expected cesarean rate for such a highly selected group of women? Lieberman *et al.*,[21] using adjustments for case mix, concluded that the expected cesarean rate for nulliparous women at gestation 36 weeks or greater and without medical risk factors should be approximately 12% compared with 24% when similar women had medical risk factors. Other investigators have studied the effects of epidural analgesia in women with characteristics similar to those included in our trial. For example, Chestnut *et al.*[22] reported overall cesarean rates of 8–10% in nulliparous women in spontaneous labor at term with singleton cephalic fetuses. Frigottelto *et al.*,[23] in a randomized trial of labor management, reported an 11% cesarean rate in nulliparous women similar to those included in our trial. Other investigators[12,13,24] have also reported cesarean rates to be 6–11% in such women. We are therefore of the view that our results can be generalized to a large and important subgroup of American women, and that concerns about the ability to generalize should not preempt our results showing that epidural analgesia does not increase cesarean births.

Although epidural analgesia was not associated with increased cesarean deliveries in our trial, it prolonged the length of the first stage of labor by approximately 40 min and was associated with a significantly increased need for oxytocin for augmentation of labor. Such prolongation of labor might have contributed to the increased incidence of maternal fever in this study, which is a known sequelae of prolonged labor. The second stage of labor was also prolonged, albeit by only approximately 10 min. Indeed, epidural analgesia has some effects on the progress of labor and increases forceps deliveries, but appropriate obstetric interventions, such as timely stimulation of labor with oxytocin, may minimize the cesarean deliveries. It is also important to emphasize that, in the case of epidural analgesia, there has been continual refinement of techniques used. Undoubtedly early methods of epidural analgesia using high doses of local anesthetic agents had greater effects on labor than contemporary techniques such as used in this trial.

In summary, epidural analgesia is an effective and popular method of relief for childbirth pain. Under the conditions of this study, we further demonstrate that labor epidural analgesia in women at term with uncomplicated pregnancies and in spontaneous active labor does not increase cesarean deliveries.

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