

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

FEBRUARY 17, 2005

VOL. 352 NO. 7

The Risk of Cesarean Delivery with Neuraxial Analgesia Given Early versus Late in Labor

Cynthia A. Wong, M.D., Barbara M. Scavone, M.D., Alan M. Peaceman, M.D., Robert J. McCarthy, Pharm.D., John T. Sullivan, M.D., Nathaniel T. Diaz, M.D., Edward Yaghmour, M.D., R-Jay L. Marcus, M.D., Saadia S. Sherwani, M.D., Michelle T. Sproviero, M.D., Meltem Yilmaz, M.D., Roshani Patel, R.N., Carmen Robles, R.N., and Sharon Grouper, B.S.

ABSTRACT

BACKGROUND

Epidural analgesia initiated early in labor (when the cervix is less than 4.0 cm dilated) has been associated with an increased risk of cesarean delivery. It is unclear, however, whether this increase in risk is due to the analgesia or is attributable to other factors.

METHODS

We conducted a randomized trial of 750 nulliparous women at term who were in spontaneous labor or had spontaneous rupture of the membranes and who had a cervical dilatation of less than 4.0 cm. Women were randomly assigned to receive intrathecal fentanyl or systemic hydromorphone at the first request for analgesia. Epidural analgesia was initiated in the intrathecal group at the second request for analgesia and in the systemic group at a cervical dilatation of 4.0 cm or greater or at the third request for analgesia. The primary outcome was the rate of cesarean delivery.

RESULTS

The rate of cesarean delivery was not significantly different between the groups (17.8 percent after intrathecal analgesia vs. 20.7 percent after systemic analgesia; 95 percent confidence interval for the difference, -9.0 to 3.0 percentage points; $P=0.31$). The median time from the initiation of analgesia to complete dilatation was significantly shorter after intrathecal analgesia than after systemic analgesia (295 minutes vs. 385 minutes, $P<0.001$), as was the time to vaginal delivery (398 minutes vs. 479 minutes, $P<0.001$). Pain scores after the first intervention were significantly lower after intrathecal analgesia than after systemic analgesia (2 vs. 6 on a 0-to-10 scale, $P<0.001$). The incidence of one-minute Apgar scores below 7 was significantly higher after systemic analgesia (24.0 percent vs. 16.7 percent, $P=0.01$).

CONCLUSIONS

Neuraxial analgesia in early labor did not increase the rate of cesarean delivery, and it provided better analgesia and resulted in a shorter duration of labor than systemic analgesia.

From the Departments of Anesthesiology (C.A.W., B.M.S., R.J.M., J.T.S., N.T.D., E.Y., R.L.M., S.S.S., M.T.S., M.Y., R.P., C.R., S.G.) and Obstetrics and Gynecology (A.M.P.), Feinberg School of Medicine, Northwestern University, Chicago. Address reprint requests to Dr. Wong at the Department of Anesthesiology, Feinberg School of Medicine, Northwestern University, 251 E. Huron, F 5-704, Chicago, IL 60611, or at c-wong2@northwestern.edu.

N Engl J Med 2005;352:655-65.

Copyright © 2005 Massachusetts Medical Society.

THE AMERICAN COLLEGE OF OBSTETRICIANS and Gynecologists recommends that “when feasible, obstetrical practitioners should delay the administration of epidural anesthesia in nulliparous women until the cervical dilatation reaches at least 4.0 to 5.0 cm and that other forms of analgesia should be used until that time.”¹ This recommendation is based on studies that found an association between the initiation of epidural analgesia early in labor and an increased rate of cesarean delivery.^{2,3} The nature of this association is uncertain. Neuraxial analgesia may directly or indirectly influence the progress of labor. Alternatively, the request for analgesia early in labor may be a marker for some other risk factor for cesarean delivery, such as dysfunctional labor.

On the basis of this recommendation, women who request analgesia early in labor frequently receive systemic opioid analgesia. However, the analgesia is often incomplete, and it has potential side effects for both the mother and the fetus, including maternal and neonatal respiratory depression, especially when neuraxial opioids are administered concomitantly.⁴

We hypothesized that initiating and maintaining neuraxial analgesia early in labor with intrathecal opioid as part of a low-dose local anesthetic technique would not increase the risk of cesarean delivery when compared with systemic opioid analgesia. We designed this trial to compare the rate of cesarean delivery in nulliparous women in spontaneous labor or with spontaneous rupture of the membranes who requested analgesia early in labor and were randomly assigned to receive intrathecal or systemic opioid analgesia.

METHODS

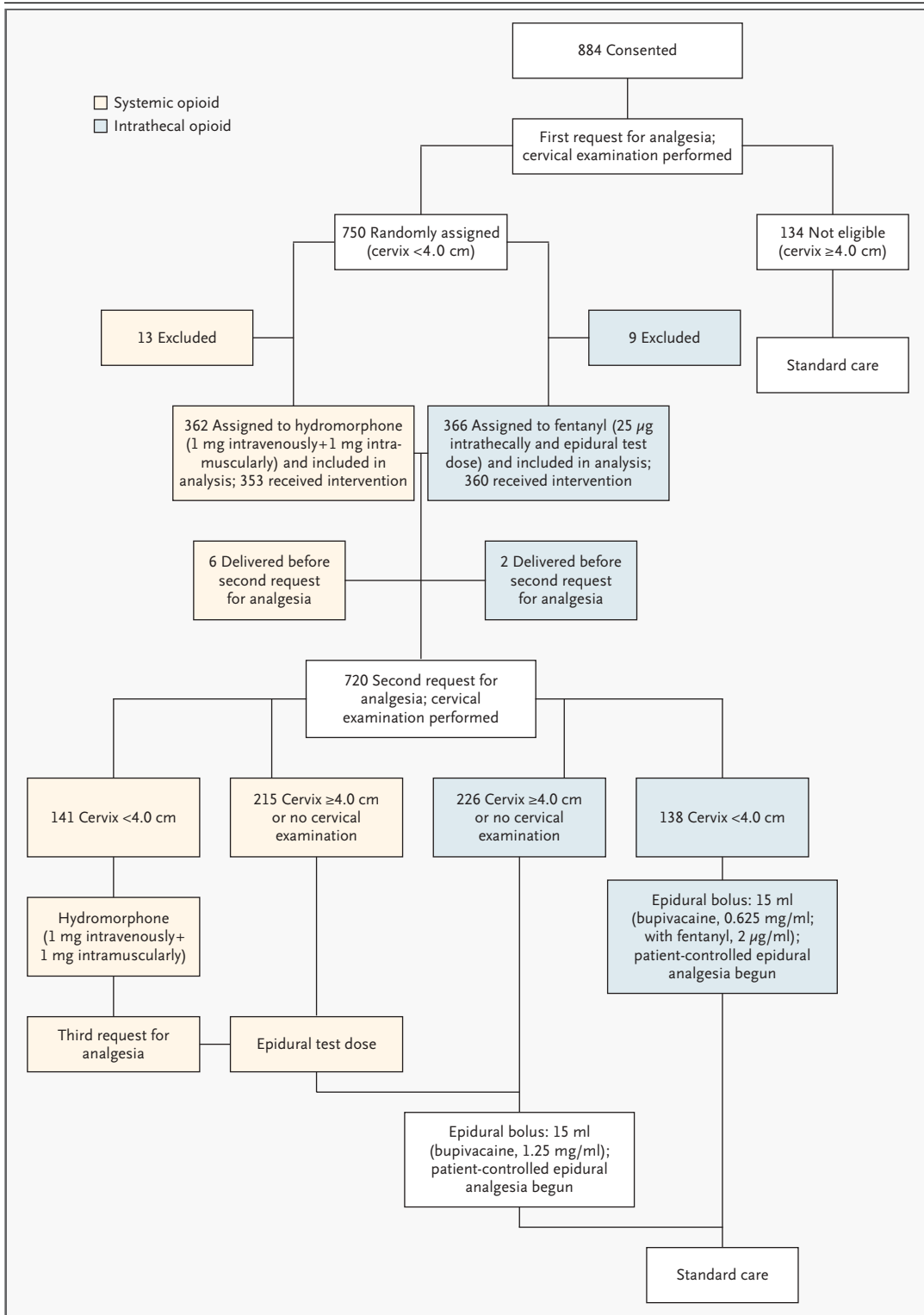
The study was approved by the Northwestern University institutional review board. All healthy nulliparous women with term, singleton pregnancies who presented in spontaneous labor or with spontaneous rupture of the membranes at Prentice Women’s Hospital in Chicago between November 2000 and December 2003 and who desired neuraxial analgesia were eligible to participate. Exclusion criteria were a nonvertex presentation, scheduled induction of labor, any contraindication to opioid analgesia, and cervical dilatation of 4.0 cm or greater. The subjects were asked to participate soon after admission and gave written informed consent before any request for analgesia.

Figure 1 (facing page). Analgesic Interventions in the Study.

The subjects received a 500-to-1000-ml fluid bolus with lactated Ringer’s solution immediately before the initiation of neuraxial analgesia. The 3-ml epidural test dose consisted of lidocaine (15 mg per milliliter) with epinephrine (5 μ g per milliliter). Standard care consisted of patient-controlled epidural analgesia with bupivacaine (0.625 mg per milliliter) and fentanyl (2 μ g per milliliter), with the following features: a basal infusion rate of 15 ml per hour, a 5-ml patient-controlled bolus, a 10-minute lockout period, and a maximal volume of 30 ml per hour. Breakthrough pain was managed with manual epidural boluses consisting of 10 to 15 ml of bupivacaine (1.25 mg per milliliter) or lidocaine (10 mg per milliliter) given by an anesthesiologist, with the epidural infusion rate increased to 20 ml per hour or the epidural-infusion concentration of bupivacaine increased to 1.1 mg per milliliter, or both. Thirteen subjects in the systemic-analgesia group were excluded from the analysis, for the following reasons: cervical diameter greater than 4.0 cm (2 subjects), induction of labor (5), twin gestation (1), breech position (1), diabetes mellitus (1), pregnancy-induced hypertension (1), incorrect study-envelope label (1), and second envelope opened (1). Nine subjects in the intrathecal-analgesia group were excluded from the analysis, for the following reasons: cervical diameter greater than 4.0 cm (2 subjects), induction of labor (6), and lost data (1). Nine subjects in the systemic-analgesia group did not receive their assigned treatment, for the following reasons: refusal of the study drug (8) and nonreassuring fetal status leading to emergency cesarean delivery before the study drug was administered (1). Six subjects in the intrathecal-analgesia group did not receive their assigned treatment, for the following reasons: refusal of the study drug (4) and use of epidural analgesia because of an inability to initiate combined spinal–epidural analgesia (2). Of the recipients of systemic analgesia whose cervical examination at the second request for analgesia revealed a diameter of less than 4.0 cm, protocol violations occurred in 11, who refused the study drug and received epidural analgesia. In 11 of the remaining subjects in this group, whose cervical dilatation was 4.0 cm or greater at the first request for analgesia, the following protocol violations occurred: no cervical examination was performed at this time and then hydromorphone was given (1); the cervical diameter was 4.0 cm or greater and then hydromorphone was given (2); or neuraxial analgesia was initiated as combined spinal–epidural analgesia (8). Of the recipients of intrathecal analgesia, protocol violations occurred in 4 at the time of the second request for analgesia: hydromorphone had been given before randomization (1), and no cervical examination was performed at the second request for analgesia and 0.625 mg per milliliter bupivacaine was given as an epidural bolus (3).

When subjects requested analgesia, the cervix was examined. If the cervix was dilated less than 4.0 cm, the subjects were randomly assigned in a

NEURAXIAL ANALGESIA IN EARLY LABOR



single block by means of a computer-generated, random-number list to either intrathecal or systemic analgesia. Group assignments were sealed in sequentially numbered, opaque envelopes that were opened only after cervical dilatation was determined to be less than 4.0 cm. Patients and care providers were not blinded to the group assignment.

ANALGESIC INTERVENTIONS AND MANAGEMENT

Analgesia was initiated in the intrathecal group by a combined spinal–epidural technique. Intrathecal fentanyl (25 µg) was injected, an epidural catheter placed, and an epidural test dose administered. At the second request for analgesia, the cervix was again examined. Epidural analgesia was then initiated as follows: if the cervix was less than 4.0 cm in diameter, a 15-ml epidural bolus of bupivacaine (0.625 mg per milliliter) with fentanyl (2 µg per milliliter) was given, and if the cervix was 4.0 cm or greater in diameter, a 15-ml epidural bolus of bupivacaine (1.25 mg per milliliter) was given (Fig. 1). In both instances, patient-controlled epidural analgesia was then begun.

Analgesia was initiated in the systemic-analgesia group with hydromorphone given intramuscularly (1 mg) and intravenously (1 mg). If the cervix was less than 4.0 cm in diameter at the second request for analgesia, these doses of hydromorphone were given again. If the cervix was 4.0 cm or greater, epidural analgesia was initiated. Epidural analgesia was given at the third analgesia request, regardless of cervical dilatation.

If no cervical examination was performed at the second request for analgesia, the cervix was assumed to be at least 4.0 cm dilated. Thereafter, patient-controlled epidural analgesia was maintained in both groups until delivery (Fig. 1).

Subjects were asked by study personnel to rate their pain according to an 11-point verbal rating score for pain (in which 0 represented no pain and 10 the worst pain imaginable) at the first and second requests for analgesia. At the second request, subjects were asked to rate their “average contraction pain” since the beginning of the analgesic intervention, as well as to rate their nausea (as none, mild, moderate, or severe) and to report any vomiting.

OBSTETRICAL MANAGEMENT

Decisions regarding obstetrical management were made by the obstetricians and midwives. Most of the subjects had continuous external electronic fe-

tal heart-rate monitoring and tocodynamometry. Internal fetal-scalp electrodes were placed when the external tracing was not interpretable. Intrauterine pressure catheters were used when necessary to document the intensity of contractions. Nurses titrated oxytocin infusions according to guidelines set by the obstetrical management team. The decision to proceed to operative delivery was made by the obstetrical team according to maternal or fetal indications. Apgar scores were assigned by personnel responsible for neonatal assessment. Umbilical-cord blood gases were measured at the discretion of the obstetrical team.

OTHER DATA

The following data about the subjects were collected: age, race (as declared by the patient), type of insurance, gestational age, weight, height, time of membrane rupture, maximal dose of oxytocin, time of complete cervical dilatation (10.0 cm), time of delivery, method of delivery (cesarean, instrumental, or spontaneous vaginal), primary indication for cesarean delivery, if applicable, and maximal maternal body temperature during labor. Fetal heart-rate tracings beginning 30 minutes before the first analgesic intervention until 30 minutes afterward were assessed by a perinatologist; patient identification was removed from the tracings, and they were not accompanied by treatment information.

OUTCOMES

The primary outcome was the method of delivery. Prespecified secondary outcomes were the indication for cesarean delivery, the method of vaginal delivery, the quality of analgesia, the use or nonuse of oxytocin, the duration of labor, the incidence of nonreassuring fetal status (i.e., fetal heart-rate patterns that do not reassure the clinician with regard to the status of the fetus), and the neonatal outcome.

STATISTICAL ANALYSIS

The study was designed to have 80 percent power to detect a difference of 50 percent in the rate of cesarean delivery, with a two-sided alpha level of 0.05. The sample size required to detect this difference was 350 subjects per group. The baseline cesarean rate (17 percent) was estimated from institutional data. The 50 percent increase in the cesarean-delivery rate was a conservative estimate based on the increased rate associated with early neuraxial analgesia observed previously in our institution.⁵ To account for expected losses in participation, 750 sub-

jects underwent randomization. A planned interim analysis after the enrollment of 225 subjects found no difference in the cesarean-delivery rate between the groups, and so the planned study recruitment was completed.⁶

Categorical data were analyzed with use of a chi-square test. Student's t-test and the Mann-Whitney U test were used to analyze interval and ordinal data. Binary logistic-regression analysis of the primary outcome was performed to identify characteristics of the subjects that were associated with cesarean delivery. The intervals from the first request for analgesia until delivery were analyzed by the Kaplan-Meier method and the log-rank test. To assess the interaction between baseline characteristics and assigned analgesia with respect to the duration of labor, a Cox regression analysis was performed. Data were analyzed according to the intention to treat. All reported P values are two-sided. A P value of less than 0.05 was required to reject the null hypothesis.

RESULTS

Eight hundred eighty-four women consented to participate (Fig. 1). One hundred thirty-four women were excluded because their cervical dilatation was 4.0 cm or greater at the first request for analgesia. Twenty-two subjects were excluded after randomization because they did not meet the inclusion criteria. The remaining 728 subjects were included in the analysis.

One hundred one obstetrical providers attended the subjects' deliveries. The median number of deliveries per provider was 7 (range, 1 to 33). The groups were similar at baseline, except that the systemic-analgesia group had a greater percentage of subjects with cervical dilatation that was less than or equal to 1.5 cm at the first request for analgesia (although the median cervical dilatation in each group was 2.0 cm, and fetal station was not significantly different between the groups); the systemic-analgesia group also had a higher incidence of spontaneous rupture of the membranes more than 12 hours before oxytocin administration (Table 1). The median cervical dilatation at the initiation of neuraxial analgesia was lower in the intrathecal-analgesia group than in the systemic-analgesia group.

LABOR AND DELIVERY OUTCOMES

The rate of cesarean delivery was not significantly different between the groups (difference in the rate after intrathecal analgesia as compared with system-

Table 1. Baseline Characteristics of the Subjects.*

Characteristic	Intrathecal Analgesia (N=366)	Systemic Analgesia (N=362)	P Value
Age — yr	31.3±5.2	31.3±5.4	0.66
Height — cm	165±7	165±7	0.93
Weight — kg	79±14	80±14	0.32
Gestational age of fetus — wk			0.84
Median	40	40	
Interquartile range	39–40	39–40	
Race — no. (%)†			0.17
Black	24 (6.6)	40 (11.0)	
Asian	13 (3.6)	17 (4.7)	
Hispanic	24 (6.6)	20 (5.5)	
White	298 (81.4)	274 (75.7)	
Other	7 (1.9)	11 (3.0)	
Private insurance (vs. public insurance) — no. (%)	339 (92.6)	329 (90.9)	0.46
Spontaneous rupture of membranes >12 hr before oxytocin infusion — no. (%)	20 (5.5)	37 (10.2)	0.02
Cervical dilatation at first request for analgesia — no. (%)			0.007
≤1.5 cm	113 (30.9)	152 (42.0)	
>1.5 to <3.0 cm	130 (35.5)	111 (30.7)	
≥3.0 cm	123 (33.6)	99 (27.3)	
Fetal station at first request for analgesia — no. (%)‡			0.10
–3.0 cm	23 (6.3)	18 (5.0)	
–2.0 cm	146 (39.9)	170 (47.0)	
–1.0 cm	169 (46.2)	137 (37.8)	
0 cm	23 (6.3)	33 (9.1)	
+1.0 cm	5 (1.4)	4 (1.1)	
Verbal rating score for pain at first request for analgesia§			0.29
Median	8	8	
Interquartile range	7–9	7–9	

* Plus-minus values are means ±SD.
 † Race was self-described by the subjects.
 ‡ The fetal station is the distance, in centimeters, of the presenting part of the fetus from the ischial spines (where minus signs denote a location above the spines and plus signs a location below the spines).
 § The verbal rating score for pain is an 11-point scale in which 0 represents no pain and 10 the worst pain imaginable.

ic analgesia, –2.9 percentage points; 95 percent confidence interval, –9.0 to 3.0; P=0.31) (Table 2). There was also no significant difference in the rate of instrumental vaginal delivery between the groups (difference, 3.6 percentage points; 95 percent con-

Table 2. Primary and Secondary Outcomes.*

Outcomes	Intrathecal Analgesia	Systemic Analgesia	P Value†	Difference (95% CI)‡
Method of delivery				
Cesarean — no./total no. (%)	65/366 (17.8)	75/362 (20.7)	0.31	-2.9 (-9.0 to 3.0)
Instrumental vaginal — no./total no. (%)	59/301 (19.6)	46/287 (16.0)	0.13	3.6 (-2.9 to 10.1)
Indications for cesarean delivery				
			0.53	
Arrest of dilatation — no./total no. (%)	31/65 (47.7)	41/75 (54.7)		-7.0 (-25.0 to 11.0)
Arrest of descent — no./total no. (%)	13/65 (20.0)	12/75 (16.0)		4.0 (-10.2 to 18.2)
Nonreassuring fetal status — no./total no. (%)	15/65 (23.1)	19/75 (25.3)		-2.3 (-17.9 to 13.4)
Other	6/65 (9.2)	3/75 (4.0)		5.1 (-4.6 to 14.8)
Other maternal outcomes				
Verbal rating score for pain at second request for analgesia§			<0.001	-3 (-3 to -3)
Median	5	8		
Interquartile range	3 to 7	7 to 9		
Average verbal rating score for pain between first and second request for analgesia§			<0.001	-4 (-5 to -3)
Median	2	6		
Interquartile range	1 to 3	4 to 7		
Duration of first analgesia — minutes			<0.001	-13 (-20 to -6)
Median	95	108		
Range	73 to 119	80 to 144		
Nausea — no. (%)			<0.001	
None	340/366 (92.9)	203/362 (56.1)		36.8 (30.8 to 42.8)
Mild	18/366 (4.9)	101/362 (27.9)		-23.0 (-28.4 to -17.6)
Moderate	7/366 (1.9)	47/362 (13.0)		-11.1 (-15.1 to -7.1)
Severe	1/366 (0.3)	11/362 (3.0)		-2.7 (-4.9 to -0.6)
Vomiting — no. (%)	7/366 (1.9)	62/362 (17.1)	<0.001	-15.2 (-19.6 to -10.8)
Cervical dilatation <4.0 cm at second request for analgesia — no./total no. (%)¶	139/317 (43.8)	141/334 (42.2)	0.67	1.6 (-6.3 to 9.6)
Cervical dilatation at initiation of neuraxial analgesia — no./total no. (%)¶				
			<0.001	
≤2.0 cm	217/366 (59.3)	41/341 (12.0)		47.3 (40.9 to 53.7)
>2.0 to 3.0 cm	133/366 (36.3)	59/341 (17.3)		19.0 (12.4 to 25.7)
>3.0 cm	16/366 (4.4)	241/341 (70.7)		-66.3 (-71.9 to -60.8)
Oxytocin infusion — no. (%)	338/366 (92.3)	342/362 (94.5)	0.38	-2.1 (-6.0 to 1.7)
Oxytocin begun after first request for analgesia — no./total no. of oxytocin infusions (%)	92/338 (27.2)	89/342 (26.0)	0.60	1.2 (-5.7 to 8.1)
Maximal oxytocin dose — mU/min			0.008	-4 (-4 to 0)
Median	14	18		
Interquartile range	10 to 22	10 to 26		

confidence interval -2.9 to 10.1; P=0.13). There were no significant differences in the indications for cesarean delivery or in the percentages of subjects who received oxytocin; however, the maximal rate of oxytocin infusion was higher in the systemic-analgesia

group. The cesarean-delivery rate was not significantly different between privately insured and publicly insured subjects (P=0.90), nor was it significantly different among different obstetrical providers (P=0.33).

Table 2. (Continued.)*

Outcomes	Intrathecal Analgesia	Systemic Analgesia	P Value†	Difference (95% CI)‡
Duration of neuraxial analgesia — min			<0.001	110 (59 to 150)
Median	440	330		
Interquartile range	306 to 596	215 to 480		
Duration of epidural analgesia — min			0.23	22 (-21 to 55)
Median	352	330		
Interquartile range	225 to 500	215 to 480		
Maximal oral temperature during labor — °C	37.3±0.5	37.3±0.5	0.06	0.13 (-0.01 to 0.28)
Neonatal outcomes				
Weight — g	3443±428	3455±431	0.85	-11 (-74 to 51)
Apgar score <7 — no. (%)				
At 1 min	61/366 (16.7)	87/362 (24.0)	0.01	-7.4 (-13.5 to -1.3)
At 5 min	5/366 (1.4)	9/362 (2.5)	0.28	-1.1 (-3.4 to 1.1)
Umbilical-cord gases measured — no. (%)	326/366 (89.1)	329/362 (90.9)	0.49	-1.8 (-6.4 to 2.8)
Umbilical-vein pH	7.30±0.06	7.30±0.06	0.99	0 (-0.01 to 0.01)
Umbilical-artery pH	7.24±0.08	7.23±0.07	0.46	0 (-0.01 to 0.02)

* Plus-minus values are means ±SD.

† P values were calculated by the chi-square or Mann-Whitney U test.

‡ The differences are the differences in the rates, medians, or means between the groups; minus signs indicate that the value was smaller in the intrathecal-analgesia group than in the systemic-analgesia group.

§ The verbal rating score for pain is an 11-point scale in which 0 represents no pain and 10 the worst pain imaginable.

¶ The denominators are less than the total number of randomly assigned subjects because some subjects delivered before the second request for analgesia or were not examined at the time of the second request for analgesia.

The median times from the initial analgesic intervention to complete dilatation and to vaginal delivery were significantly shorter after intrathecal analgesia than after systemic analgesia (Fig. 2). The use of intrathecal rather than systemic analgesia predicted a shorter interval to complete cervical dilatation, even after adjustment for cervical dilatation and fetal station at the time the analgesic intervention was begun and for other potential confounders (data not shown). There were no significant differences between the groups in the duration of the second stage of labor or in the time to delivery in subjects who delivered by cesarean section.

OTHER OUTCOMES

The average pain score between the first and second requests for analgesia was significantly lower in the intrathecal-analgesia group than in the systemic-analgesia group, but the interval between the first and second requests was longer in the systemic-analgesia group (Table 2). The incidence of nausea and vomiting and the severity of nausea were lower in the intrathecal-analgesia group. There was no significant difference in the maximal temperature

during labor. However, the duration of neuraxial analgesia was longer in the intrathecal-analgesia group.

The incidence of fetal heart-rate tracings that would lead to an obstetrical intervention if observed in real time by the perinatologist (referred to here as nonreassuring tracings) was not significantly different between the groups either before or after the initiation of analgesia (Table 3). There was a higher incidence of prolonged and late decelerations in heart rate in the intrathecal group after the initiation of analgesia. One subject in the systemic-analgesia group had a cesarean delivery because of prolonged deceleration of the fetal heart rate after randomization, but before she had received analgesia. Neonatal outcomes were not significantly different between the groups, except that there was a greater incidence of one-minute Apgar scores below 7 in the systemic-analgesia group (Table 2).

Baseline variables significantly associated with cesarean delivery in the multivariate analysis included age (relative risk for each one-year increase, 1.02; 95 percent confidence interval, 1.00 to 1.03), height (relative risk for each 1-cm increase, 1.05; 95 per-

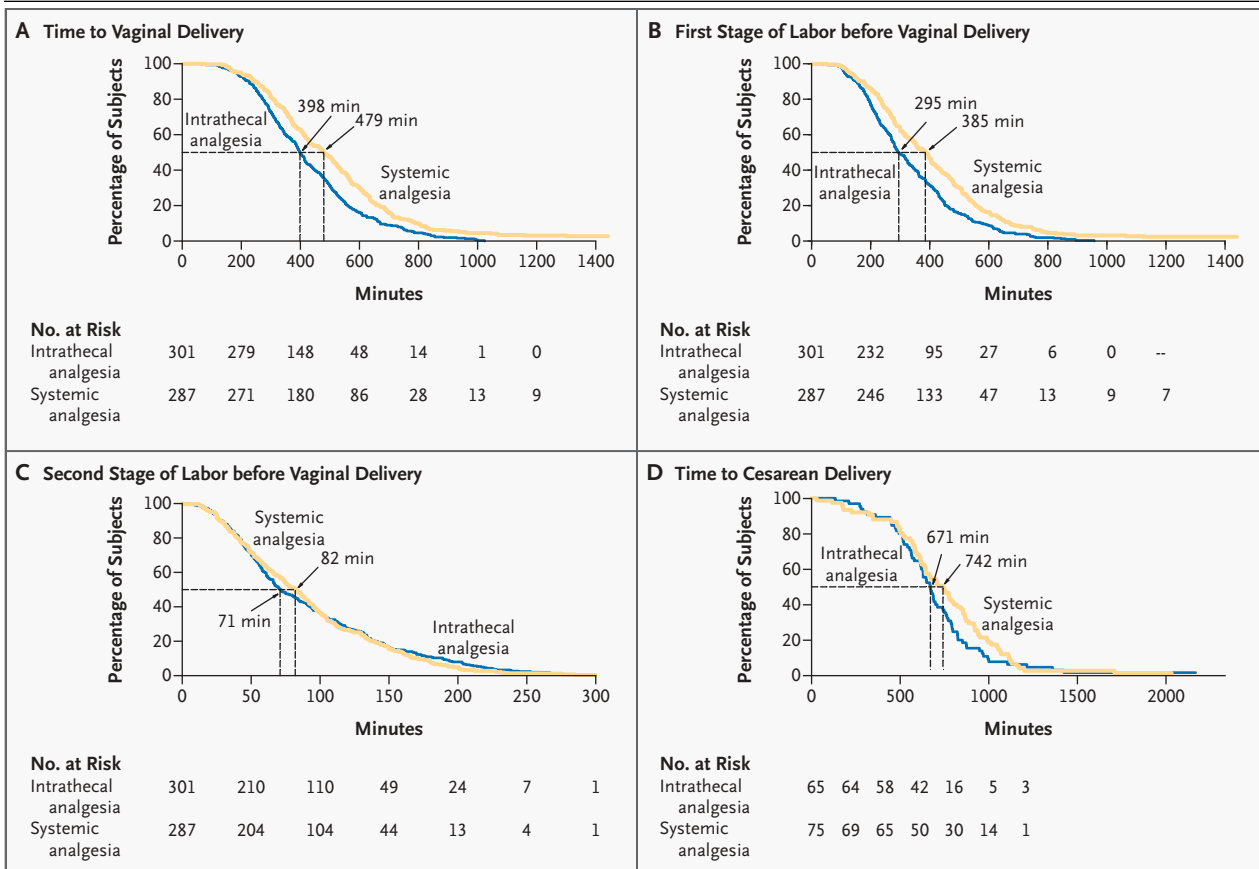


Figure 2. Kaplan–Meier Curves for the Duration of Labor.

Arrows indicate median values. Panel A shows the time to delivery among subjects who delivered vaginally. The difference in the median time to delivery between the intrathecal-analgesia group and the systemic-analgesia group was –81 minutes (95 percent confidence interval for the difference, –123 to –28 minutes; $P<0.001$). Panel B shows the duration of the first stage of labor among subjects who delivered vaginally. The difference in the median time between the intrathecal-analgesia group and the systemic-analgesia group was –90 minutes (95 percent confidence interval for the difference, –123 to –35 minutes; $P<0.001$). In Panels A and B, time 0 is the time of the initiation of analgesia. Panel C shows the duration of the second stage of labor (complete cervical dilatation to delivery) among subjects who delivered vaginally. The difference in the median time between the intrathecal-analgesia group and the systemic-analgesia group was –11 minutes (95 percent confidence interval for the difference, –21 to 6 minutes; $P=0.67$). Panel D shows the time to delivery among subjects who delivered by cesarean section. The difference in the median time between the intrathecal-analgesia group and the systemic-analgesia group was –71 minutes (95 percent confidence interval for the difference, –176 to 46 minutes; $P=0.23$).

cent confidence interval, 1.01 to 1.08), weight (relative risk for each 1-kg increase, 1.02; 95 percent confidence interval, 1.01 to 1.03), and maximal oxytocin-infusion rate (relative risk for each increase by 1 mU per minute, 1.05; 95 percent confidence interval, 1.02 to 1.07). The method of providing analgesia was not a significant independent predictor of cesarean delivery.

DISCUSSION

In this randomized trial, intrathecal opioid analgesia, as compared with systemic opioid analgesia, in

early labor did not increase the rate of cesarean delivery. These results extend those reported by Chestnut et al., who found no difference in the cesarean-delivery rate between nulliparous women randomly assigned to early epidural analgesia (at a cervical dilatation of greater than 3.0 cm but less than 5.0 cm) or late epidural analgesia (at a cervical dilatation of 5.0 cm or greater after systemic opioid administration).^{7,8} In these studies, the median cervical dilatation in the early groups was 3.5 and 4.0 cm, as compared with 2.0 cm in the current study. Similarly, in a study of 60 nulliparous women, no difference in the cesarean-delivery rate was found be-

Table 3. Fetal Heart-Rate Patterns.*

Pattern	Before Analgesia			After Analgesia		
	Intrathecal (N=362)	Systemic (N=358)	P Value	Intrathecal (N=362)	Systemic (N=358)	P Value
	no. (%)			no. (%)		
Variability			0.03			0.005
Absent	0	1 (0.3)		0	2 (0.6)	
Decreased	0	6 (1.7)		2 (0.6)	13 (3.6)	
Normal	362 (100.0)	351 (98.0)		360 (99.4)	343 (95.8)	
Increased	0	0		0	0	
Nonreassuring change				2 (0.6)	8 (2.2)	0.05
Prolonged decelerations	1 (0.3)	1 (0.3)	0.99	14 (3.9)	2 (0.6)	0.003
Persistent variable decelerations			0.42			0.24
None	356 (98.3)	347 (96.9)		342 (94.5)	347 (96.9)	
Mild	5 (1.4)	10 (2.8)		17 (4.7)	10 (2.8)	
Moderate	1 (0.3)	1 (0.3)		3 (0.8)	1 (0.3)	
Severe	0	0		0	0	
Nonreassuring change				14 (3.9)	4 (1.1)	0.02
Late decelerations present	5 (1.4)	3 (0.8)	0.49	19 (5.2)	7 (2.0)	0.02
Nonreassuring change				15 (4.1)	4 (1.1)	0.01
Reassuring tracing	345 (95.3)	340 (95.0)	0.84	336 (92.8)	337 (94.1)	0.48
Contraction frequency >10 per 20 min	6 (1.7)	3 (0.8)	0.32	5 (1.4)	3 (0.8)	0.49
Contraction duration >70 sec	4 (1.1)	4 (1.1)	0.99	5 (1.4)	5 (1.4)	0.99

* The fetal heart-rate tracings from eight subjects could not be located. Fetal heart-rate tracings were assessed as follows: Variability was graded as absent (≤ 2 beats per minute), decreased (3 to 5 beats per minute), normal (6 to 25 beats per minute), or increased (> 25 beats per minute). The presence of prolonged decelerations (< 100 beats per minute for > 60 seconds) was noted. Variable decelerations were graded as none, mild (< 30 seconds irrespective of rate or > 80 beats per minute irrespective of duration), moderate (< 70 beats per minute between 30 and 60 seconds or 70 to 80 beats per minute for > 60 seconds), or severe (< 70 beats per minute for > 60 seconds). Late decelerations were determined to be present or absent. The tracings before and after analgesia were assessed as reassuring or nonreassuring (i.e., as patterns that would lead to an obstetrical intervention if observed in real time by the perinatologist). Decreases in variability, a worsening of persistent variable decelerations, and the appearance of late decelerations after analgesia in a case in which none were present before analgesia were considered negative changes. Contraction frequency (> 10 per 20 minutes) and duration (> 70 seconds) were also recorded. A nonreassuring change was a change to a less reassuring pattern after the initiation of analgesia.

tween those who received epidural analgesia early and those who received it late (mean cervical dilatation, 2.3 cm and 4.5 cm, respectively).⁹

The absence of an association between neuraxial analgesia given early in labor and an increased cesarean-delivery rate suggests that an early request for analgesia, or increased use of analgesics early in labor, may be markers for other risk factors for cesarean delivery.^{10,11} Presumably, women who have more pain and require more analgesia are at increased risk for cesarean delivery. For example, fetal macrosomia, a risk factor for cesarean delivery, was associated with a greater rate of breakthrough pain during epidural analgesia.¹² The requirements for

epidural local anesthetics were higher among women who underwent cesarean delivery for dystocia than in women who delivered vaginally.¹³

A clinically important finding of the current study is that the duration of the first stage of labor was approximately 90 minutes shorter after intrathecal opioid administration than after systemic opioid administration. Previous studies have found that epidural, as compared with systemic opioid, analgesia is associated with a prolonged first stage of labor.^{2,14} Factors that influence the progress of labor are not well understood. Autonomic imbalance has been proposed as an explanation of the association between epidural analgesia and pro-

longed labor.¹⁵ Tocodynamic parasympathetic efferent nerves are blocked by neuraxial local anesthetics, but presumably not by neuraxial opioids. This difference may explain why cervical dilation was faster in women who were randomly assigned to combined spinal–epidural analgesia as compared with those assigned to epidural analgesia.¹⁶ Furthermore, the presence or degree of autonomic imbalance may be influenced by the type of epidural analgesia (for example, the concentration of local anesthetics). In the current study, epidural analgesia was not identical among all the subjects, and this discrepancy may have been a factor in the observed difference in the progress of labor.

Analgesia may have indirect effects on the progress of labor. Intrathecal fentanyl decreased the maternal concentration of circulating epinephrine,¹⁷ but systemic meperidine did not.¹⁸ It is possible that the decrease in circulating epinephrine levels associated with intrathecal analgesia decreases epinephrine-induced tocolysis, resulting in faster labor. An alternative explanation is that systemic opioid analgesia negatively influences the progress of labor. Opioids decreased uterine activity both in humans in active labor¹⁹ and in pregnant baboons.²⁰

The prolonged infusion of an epidural anesthetic may result in motor blockade and may increase the risk of instrumental vaginal delivery.²¹ In the current study, the rate of instrumental vaginal delivery was not significantly different between the groups, although the subjects in the intrathecal group received neuraxial analgesia for a longer period. Neuraxial analgesia initiated with an opioid and maintained with low-dose epidural bupivacaine is unlikely to result in motor blockade.

A positive association between epidural analgesia and the use of oxytocin to augment labor has been reported.²² We did not find a difference between the groups in the rate of oxytocin use, but most of the subjects received oxytocin before their first request for analgesia — a finding consistent with our pattern of institutional practice. Women who received systemic opioids early in labor required a higher oxytocin-infusion rate than those who received intrathecal opioids, perhaps because of slower labor progress.

The authors of a meta-analysis comparing intrathecal with nonintrathecal techniques for administering opioid neuraxial analgesia concluded that intrathecal opioid analgesia was associated with fetal bradycardia.²³ In the current study, prolonged,

persistent variable, and late fetal heart-rate decelerations developed within 30 minutes after the first analgesic intervention more often in the intrathecal-analgesia group than in the systemic-analgesia group. However, the incidence of an unfavorable fetal heart rate was low, did not differ between groups, and did not result in any adverse neonatal outcomes or in the need for emergency cesarean delivery.

In a previous study, neonates delivered by women randomly assigned to receive systemic opioid analgesia had lower one-minute Apgar scores than neonates whose mothers received epidural analgesia.²⁴ Although both groups in the current study received epidural analgesia, neonates in the systemic-analgesia group were more likely than those in the intrathecal-analgesia group to have low one-minute Apgar scores, even though the opioid was administered early in labor, usually hours before delivery.

Epidural analgesia lasting more than five hours in women in labor is associated with elevated maternal temperature.^{25,26} Although women randomly assigned to early intrathecal analgesia had neuraxial analgesia for a longer duration than those assigned to systemic analgesia, the maximal temperature during labor was not significantly different between the groups.

There are several limitations to our study. The study was not powered to detect a small difference between the groups in the rate of cesarean delivery. However, the 95 percent confidence interval for the difference between the groups suggests that plausible differences between the groups would not exceed 9 percentage points if the rate in the intrathecal group were lower or 3 percentage points if the rate in the intrathecal group were higher. We studied nulliparous women in spontaneous labor or with spontaneous rupture of the membranes, and our results may not apply to other populations. In addition, the faster progress of labor after intrathecal analgesia, as compared with systemic analgesia, may have been influenced by the greater cervical dilatation at the initiation of analgesia. Multivariate modeling, however, indicated that the type of analgesia was an independent predictor of the progress of labor.

Different obstetrical providers and management styles (including the pattern of oxytocin use) may influence the outcome of labor, and we did not adjust for these factors. Finally, the study was not blinded. It is unlikely, however, that knowledge of the type of analgesia biased obstetricians' decisions regarding the method of delivery. Cesarean deliveries were

performed only when there was arrest of dilatation or arrest of descent or when the fetal status was nonreassuring, and none of these factors were associated with the type of analgesia.

Techniques for administering neuraxial analgesia during labor vary, and various techniques may affect the outcome of labor differently. For example, epidural analgesia consisting of bupivacaine at a dose of 2.5 mg per milliliter resulted in a higher rate of instrumental vaginal delivery than bupivacaine at a dose of 0.625 mg per milliliter with fentanyl.²¹ The results obtained with these analgesia regimens may not be applicable to other regimens. Similarly, opioids have been observed in vitro to have differ-

ent effects on uterine contractile activity.^{27,28} It is not clear whether these differences exist in vivo as well.

In summary, the results of this randomized trial suggest that nulliparous women in spontaneous labor or with spontaneous rupture of membranes who request pain relief early in labor can receive neuraxial analgesia at that time without adverse consequences. When compared with systemic opioid analgesia, initiation of early neuraxial analgesia does not increase the risk of cesarean delivery and may shorten labor.

Supported by the Department of Anesthesiology, Feinberg School of Medicine, Northwestern University.

We are indebted to our obstetrics, nursing, and anesthesiology colleagues for their support and assistance during this study.

REFERENCES

- Goetzl LM. ACOG Practice Bulletin no. 36: clinical management guidelines for obstetrician-gynecologists: obstetric analgesia and anesthesia. *Obstet Gynecol* 2002; 100:177-91.
- Thorp JA, Hu DH, Albin RM, et al. The effect of intrapartum epidural analgesia on nulliparous labor: a randomized, controlled, prospective trial. *Am J Obstet Gynecol* 1993; 169:851-8.
- Nageotte MP, Larson D, Rumney PJ, Sidhu M, Hollenbach K. Epidural analgesia compared with combined spinal-epidural analgesia during labor in nulliparous women. *N Engl J Med* 1997;337:1715-9.
- Hughes SC. Respiratory depression following intraspinal narcotics: expect it! *Int J Obstet Anesth* 1997;6:145-6.
- Seyb ST, Berka RJ, Socol ML, Dooley SL. Risk of cesarean delivery with elective induction of labor at term in nulliparous women. *Obstet Gynecol* 1999;94:600-7.
- Wong CA, Scavone BM, Sullivan JT, et al. Randomized trial of neuraxial vs. systemic analgesia for latent phase labor: effect on incidence of Cesarean delivery. *Anesthesiology* 2002;96:Suppl 1:01-1. abstract.
- Chestnut DH, McGrath JM, Vincent RD Jr, et al. Does early administration of epidural analgesia affect obstetric outcome in nulliparous women who are in spontaneous labor? *Anesthesiology* 1994;80:1201-8.
- Chestnut DH, Vincent RD Jr, McGrath JM, Choi WW, Bates JN. Does early administration of epidural analgesia affect obstetric outcome in nulliparous women who are receiving intravenous oxytocin? *Anesthesiology* 1994;80:1193-200.
- Luxman D, Wolman I, Groutz A, et al. The effect of early epidural block administration on the progression and outcome of labor. *Int J Obstet Anesth* 1998;7:161-4.
- Alexander JM, Sharma SK, McIntire DD, Wiley J, Leveno KJ. Intensity of labor pain and cesarean delivery. *Anesth Analg* 2001; 92:1524-8.
- Hess PE, Pratt SD, Soni AK, Sarma MC, Oriol NE. An association between severe labor pain and cesarean delivery. *Anesth Analg* 2000;90:881-6.
- Hess PE, Pratt SD, Lucas TP, et al. Predictors of breakthrough pain during labor epidural analgesia. *Anesth Analg* 2001;93: 414-8.
- Panni MK, Segal S. Local anesthetic requirements are greater in dystocia than in normal labor. *Anesthesiology* 2003;98:957-63.
- Halpern SH, Leighton BL, Ohlsson A, Barrett JFR, Rice A. Effect of epidural vs parenteral opioid analgesia on the progress of labor: a meta-analysis. *JAMA* 1998;280: 2105-10.
- Leighton BL, Halpern SH, Wilson DB. Lumbar sympathetic blocks speed early and second stage induced labor in nulliparous women. *Anesthesiology* 1999;90:1039-46. [Erratum, *Anesthesiology* 1999;91:602.]
- Tsen LC, Thue B, Datta S, Segal S. Is combined spinal-epidural analgesia associated with more rapid cervical dilation in nulliparous patients when compared with conventional epidural analgesia? *Anesthesiology* 1999;91:920-5.
- Cascio M, Pygon B, Bernett C, Ramanathan S. Labour analgesia with intrathecal fentanyl decreases maternal stress. *Can J Anaesth* 1997;44:605-9.
- Neumark J, Hammerle AF, Bieglmayer C. Effects of epidural analgesia on plasma catecholamines and cortisol in parturition. *Acta Anaesthesiol Scand* 1985;29:555-9.
- Petrie RH, Yeh S, Barron BA, et al. Dose-response effects of intravenous meperidine on uterine activity. *J Maternal Fetal Med* 1993;2:159-64.
- Kowalski WB, Parsons MT, Pak SC, Wilson L Jr. Morphine inhibits nocturnal oxytocin secretion and uterine contractions in the pregnant baboon. *Biol Reprod* 1998;58: 971-6.
- Comparative Obstetric Mobile Epidural Trial (COMET) Study Group UK. Effect of low-dose mobile versus traditional epidural techniques on mode of delivery: a randomised controlled trial. *Lancet* 2001;358:19-23.
- Gambling DR, Sharma SK, Ramin SM, et al. A randomized study of combined spinal-epidural analgesia versus intravenous meperidine during labor: impact on cesarean delivery rate. *Anesthesiology* 1998;89: 1336-44.
- Mardirosoff C, Dumont L, Boulvain M, Tramer MR. Fetal bradycardia due to intrathecal opioids for labour analgesia: a systematic review. *BJOG* 2002;109:274-81.
- Sharma SK, Alexander JM, Messick G, et al. Cesarean delivery: a randomized trial of epidural analgesia versus intravenous meperidine analgesia during labor in nulliparous women. *Anesthesiology* 2002;96:546-51.
- Lieberman E, Lang JM, Frigoletto F Jr, Richardson DK, Ringer SA, Cohen A. Epidural analgesia, intrapartum fever, and neonatal sepsis evaluation. *Pediatrics* 1997;99: 415-9.
- Camann WR, Hortvet LA, Hughes N, Bader AM, Datta S. Maternal temperature regulation during extradural analgesia for labour. *Br J Anaesth* 1991;67:565-8.
- Sivalingam T, Pleuvry BJ. Actions of morphine, pethidine and pentazocine on the oestrus and pregnant rat uterus in vitro. *Br J Anaesth* 1985;57:430-3.
- Yoo KY, Lee J, Kim HS, Jeong SW. The effects of opioids on isolated human pregnant uterine muscles. *Anesth Analg* 2001;92: 1006-9.

Copyright © 2005 Massachusetts Medical Society.