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Primary versus *Secondary Outcomes in Gargantuan Studies*

EPIDURAL analgesia is currently the most effective method available to treat pain in labor. Retrospective studies conducted during the 1980s and 1990s suggested that epidural analgesia might slow the progress of labor and cause unnecessary Cesarean sections.[1] Unfortunately, retrospective study cannot readily separate cause and effect. If patients with slower labor are more likely to receive epidural anesthesia, then a retrospective study may identify an association between epidural anesthesia and slowed labor, but it does not establish a causal link.

Causality is only established by a prospective, double-blind, randomized trial. Unless there is a failure of blinding or randomization, all confounding variables (*e.g.*, slower labor on enrollment into the trial), including the "unknown unknowns," are evenly divided between the treatment groups. A difference in outcome can only be explained by the difference in treatments, establishing causality. Thus, recent randomized prospective studies[2,3] have dispelled the notion that early initiation of epidural anesthesia increases in the risk of Cesarean section. The question remains, however, how early can an epidural be placed without enhancing the risk of Cesarean delivery. In this issue of ANESTHESIOLOGY, Wang *et al.* definitively address this question in the largest randomized, prospective clinical trial of labor epidural ever conducted at a single center.[4]

The authors randomly assigned 12,793 nulliparous women who requested analgesia at 1-cm cervical dilation or less to receive an "early epidural" when they reached 1-cm dilation or a "late epidural" after 4-cm cervical dilation. The women were treated with meperidine until the assigned cervical dilation was reached. The primary outcome variable, the rate of Cesarean delivery, did not differ between the groups. The time from randomization (at first request for analgesia) to delivery was not different. Lastly, there was no increase in the rate of instrumental vaginal delivery. The large size, prospective randomized design, and unambiguous outcome measures definitively demonstrate that there is no clinically important relationship between epidural anesthesia given as early as 1-cm cervical dilation and (1) Cesarean delivery, (2) labor duration, and (3) rate of instrumentation. As such, the safe period for epidural analgesia has now been pushed back to 1-cm dilation.

Bigger is not always better though. Every study entails risk. In this case withholding epidurals created the risk of lower satisfaction. The authors state that they designed their study to be able to detect a difference in the rate of Cesarean section of 2.3%. It is arguable whether this is a reasonable difference to target. In this case, the authors anticipated proving the null hypothesis. This trial should have been designed to prove "noninferiority" within a reasonable confidence interval.

The authors measured 29 secondary outcomes. The interpretation of statistically significant secondary outcomes can be complex, particularly when the primary outcome does not demonstrate statistical significance, as in this case.[5,6] A trial this large may detect relatively small difference in secondary outcomes that are clinically trivial or even spurious. For example, the authors followed up with the patients 6 weeks after delivery on breastfeeding success. Early epidural was strongly associated with less success with breastfeeding ($P < 0.0001$). Despite the strength of the statistical association, the difference between the two groups was modest (70% success in the early epidural group compared to 78% success in the late epidural group). The physiologic mechanism for breastfeeding problems caused by the difference between 4.8 and 12.6 h of exposure to epidural ropivacaine and sufentanil is difficult to imagine. It is difficult to interpret multiple secondary endpoints in a randomized clinical trial; despite the very low *P* value, this finding should be considered a novel hypothesis generated by this study that requires further follow-up as a primary endpoint in a subsequent randomized controlled trial. The authors have undertaken this exercise, and their findings are sure to be important.

There are several additional anomalies among the secondary endpoints. For example, the Visual Analog Scale scores in patients receiving an epidural at 1 cm were similar to those in women receiving opioids until the epidural was placed at 4 cm. This seems surprising; a properly functioning epidural should be almost completely effective at blocking labor pain. Although the Visual Analog Scale scores were similar, maternal satisfaction was significantly higher in the early epidural group (84 *vs.* 62, $P < 0.01$). Perhaps the difference in maternal satisfaction was the result of a true difference in pain that was obscured by intersubject variability, or perhaps the difference was the result of

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increased likelihood of nausea and vomiting in the late epidural group.

Other groups have found an increased incidence of maternal fever related to epidural analgesia.[7] In the study by Wang *et al.*, earlier epidural placement was not a risk factor for maternal fever. The authors found no difference in maternal temperature between groups or any difference in the incidence of neonatal sepsis work-ups.

Prospective randomized trials of this size are not common in our specialty. The study by Wang *et al.* illustrates both the strength and potential weaknesses of such studies. The strength is that the primary endpoint can be established with great certainty, permitting as assessment of causality. The disadvantage is that for (very unintuitive) statistical reasons, there is a risk of spurious associations being identified among the secondary endpoints. The conservative view is to accept the primary endpoints as definitive and view any associations seen with the secondary endpoints with caution, particularly if a causative mechanism is not evident.

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Epidural Analgesia in the Latent Phase of Labor and the Risk of Cesarean Delivery

A Five-year Randomized Controlled Trial

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Background: **The optimal timing of epidural analgesia has been a controversial issue, and how early women can benefit from epidural analgesia is still debated. The objective of this trial was to test the hypothesis that patient-controlled epidural analgesia given at cervical dilation of 1.0 cm or more does not increase the risk of prolonged labor or Cesarean delivery.**

Methods: **After institutional review board approval and patient consent, 12,793 nulliparous patients requesting neuraxial analgesia were enrolled and randomized to an early epidural (cervical dilation at least 1.0 cm) or delayed epidural (cervical dilation at least 4.0 cm) group. A 15-ml epidural analgesic mixture consisting of 0.125% (1.25 mg/ml) ropivacaine plus 0.3 μg/ml sufentanil was given in a single bolus, followed by patient-controlled pump with a 10-ml bolus without background infusion. Repeatable meperidine (25 mg) was prescribed as being the rescue analgesic to patients in the delayed epidural group. The primary outcome was the rate of Cesarean section.**

Results: **The median diameters of cervical dilation were 1.6 cm and 5.1 cm in the early and delayed epidural groups, respectively ($P < 0.0001$). The duration of labor from analgesia request to vaginal delivery was equal in both groups (11.3 ± 4.5 h for early epidural and 11.8 ± 4.9 h for delayed epidural group women, $P = 0.90$). No statistically significant difference in the rate of Cesarean section was observed between the two groups on the intention-to-treat analysis (23.2% *vs.* 22.8% in the early and delayed epidural groups, respectively; $P = 0.51$).**

Conclusions: **Epidural analgesia in the latent phase of labor at cervical dilation of 1.0 cm or more does not prolong the progression of labor and does not increase the rate of Cesarean in nulliparous women compared with the delayed analgesia at the cervical dilation of 4.0 cm or more.**

NEURAXIAL analgesia is the most effective treatment available for pain control during labor and delivery, and it is a preferable method because it can provide more effective pain relief compared with nonneuraxial pharmacological analgesia.[1] However, optimal timing of epidural analgesia (EA) has been a controversial issue and how early in the latent phase of labor can women benefit from epidural is still debated. Before 2002, clinical guidelines recommended that the administration of EA in nulliparous women should be delayed until the cervical dilation reaches at least 4.0 to 5.0 cm and that other forms of analgesia should be used until that time.[2] In 2005, Wong *et al.* published a paper clarifying that pain relief early in labor with neuraxial analgesia at the cervix dilated 2.0 cm or more does not increase the risk of Cesarean delivery[3]; this combined with Ohel's report[4] contributed to the change in recommendation on EA in labor pain control from the American College of Obstetricians and Gynecologists in June 2006.[5]

The current best available evidence in nulliparous women at term with singleton fetus in vertex presentation supports that EA is safe in laboring women with cervix dilated 2 cm or more,[3,4] and systematic reviews on this topic suggest improved definition of dystocia and nonreassuring fetal status diagnoses with precise and repeatable criteria.[1,6,7] The National Institute for Health and Clinical Excellence guidelines[8,9] suggest that "women in labor who desire regional analgesia should not be denied it, including women in severe pain in the latent first stage of labor – a period of time begins from painful contractions and some cervical change, including cervical effacement and dilation up to 4 cm. However, data in its finding-review section do not address the indication when cervical dilation is less than 2.0 cm.

The current randomized controlled trial was designed to test the hypothesis that patient-controlled epidural analgesia in women requesting and receiving early labor analgesia in the latent phase of labor (at least 1.0 cm cervical dilation)

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do not have an increased risk of prolonged labor or Cesarean section (CS) compared to women who are assigned to wait for a cervical dilation of at least 4.0 cm.

Materials and Methods

Participants and Ethics

After approval by the institution's Ethics Examining Committee of Human Research (the Affiliated Nanjing Maternity and Child Health Care Hospital, Nanjing Medical University, Nanjing, Jiangsu, China), all healthy nulliparous women who spontaneously went into labor at term requesting labor analgesia were screened for eligibility. All included participants were asked to participate in the study soon after admission to the delivery suite and signed an informed consent before randomization. If the woman did not want an epidural, we reassigned her to receive alternative methods for labor pain control. A full explanation was given to those willing to accept epidural analgesia with respect to epidural puncture and catheterization, the opioid and local anesthetics used in this study, and the linear Visual Analog Scale (VAS) of pain and satisfaction with analgesia. The data were collected between January 2003 and December 2007 at the Nanjing Medical University–affiliated tertiary teaching hospital in China. Hospital teaching status was ascertained from the Council of Teaching Hospitals of Chinese Medical Colleges. During the whole recruitment course, the labor epidural rate in our institution is 80% on average in nulliparous women.

Randomization

When patients requested analgesia, the cervical examination was performed by obstetricians. If the cervical dilation was 1.0 cm or greater in diameter, the subjects were assigned by a completely random allocation in a single block to either the latent phase analgesia with cervix at least 1.0 cm or the active phase analgesia with cervix at least 4.0 cm. The random number list was generated by means of the QuickCalcs# (GraphPad Software Inc., La Jolla, San Diego, CA). The group assignment numbers were sealed in an envelope and kept by the study supervisor. After the written consent was signed and a cervical dilation was examined to be 1.0 cm or greater, then the opaque envelope was unsealed to determine which analgesic technique would be performed. The healthcare providers, data-collecting members, and parturients were not masked to the group allocation except for data-analyzing members.

Demographic Characteristics

The following data were collected as demographic characteristics of the subjects: age at delivery, weight, height, gestational age of fetus, current status of smoking, whether spontaneous rupture of the membrane more than 12 h before oxytocin infusion, and VAS rating of pain intensity before any analgesia.

Exclusion Criteria

Parturients were excluded from the study if one or more of the following criteria were met: (1) allergy to opioids, a history of the use of centrally–acting drugs of any sort, chronic pain, and psychiatric diseases records; (2) participants younger than 18 yr or older than 45 yr; (3) those who were not willing to or could not finish the whole study; (4) alcohol- or opioid-dependent patients were excluded for their influence on the analgesic efficacy of the epidural analgesics; (5) subjects with a nonvertex presentation or scheduled induction of labor; (6) diagnosed diabetes mellitus and pregnancy-induced hypertension; (7) twin gestation and breech presentation.

Subjects who did not request any analgesic procedures (see Table 1, Supplemental Digital Content 1, which is a table listing all possible reasons for nonanalgesia request in Chinese population, http://links.lww.com/ALN/A543) were not enrolled into the study, and they were still treated with standard obstetric care procedures according to clinical indications (see Table 2, Supplemental Digital Content 2, which is a table listing the procedures of standard obstetric care, http://links.lww.com/ALN/A544). Even so, the systemic or epidural analgesia was still available to them if they wanted an expostanalgesia based on the individual request. In case the standard epidural analgesia was used, the technique was performed by nonstudy members, and the corresponding data were not analyzed in this trial.

Analgesia Design

Cervix of parturient admitted into the delivery room was examined after analgesia request. If the cervical dilation was less than 1.0 cm, 25 mg of meperidine was prescribed intramuscularly as being the rescue analgesic until cervical dilation of at least 1.0 cm, and repeatable 25-mg meperidine could be given intramuscularly if the pain control was inadequate at the patient's request; if the cervical dilation was at least 1.0 cm, the parturients were randomly assigned into one of two groups by means of a random-number list: group of latent phase analgesia (cervical dilation of at least 1.0 cm) and group of active phase analgesia (cervical dilation of at least 4.0 cm) (see flowchart in fig. 1). Definitions of the first and second stages of labor are adapted from the National Institute for Health and Clinical Excellence guidelines[8] and reports elsewhere.[10] If a patient with the cervical dilation less than 4.0 cm was randomized into active group, 25 mg of meperidine was prescribed intramuscularly as being the rescue analgesic until the dilation reached 4.0 cm or more, and repeatable 25-mg meperidine could be given intramuscularly if the pain control

Online Calculators for Scientists, available at http://www.graphpad.com/quickcalcs/RandMenu.cfm; accessed May 6, 2009.

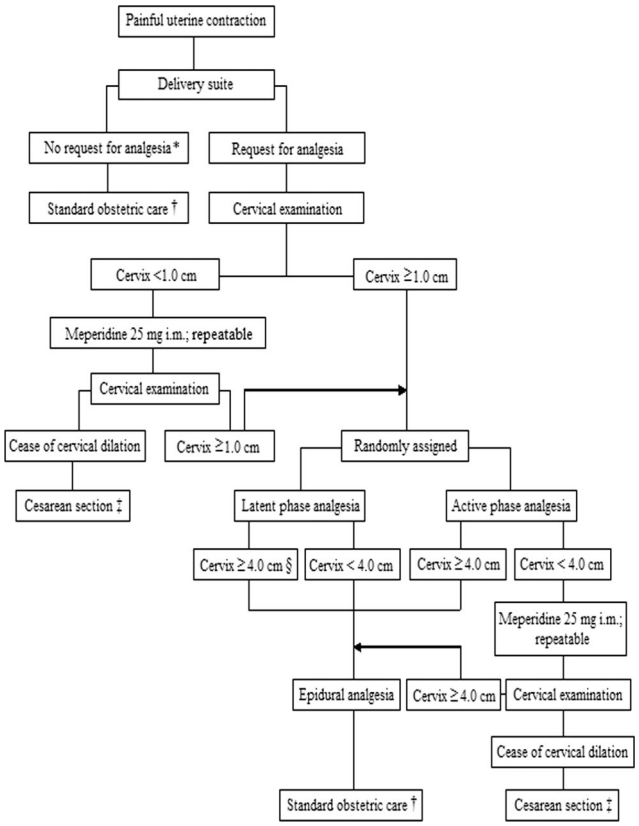

Fig. 1. Selection flow of the study participants. The major reasons for exclusion and lost follow–up were presented in the result part in the text. * See reasons for nonanalgesia request in the table, Supplemental Digital Content 1; † see standard obstetric care procedures in the table, Supplemental Digital Content 2; ‡ see indications of cesarean section in the table, Supplemental Digital Content 2; § denotes protocol violation occurred of these patients, *i.e.*, subjects with cervical dilation ≥ 4.0 cm were randomly assigned into the latent phase analgesia group. i.m. = intramuscularly.

was inadequate at the patient's request. Epidural puncture and catheterization was performed to all participants after cervical examination by the obstetricians or midwives. The test dose of 3.0 ml of lidocaine 1.5% (45 mg) plus 5 μg/ml epinephrine was given to both groups. After delivering a test dose, all participants received a 15-ml epidural analgesic mixture in a single bolus of 0.125% (1.25 mg/ml) ropivacaine with 0.3 μg/ml sufentanil followed by patient-controlled analgesic pump with a 10-ml patient-controlled bolus without background infusion, a lockout interval of 15 min, and hourly limit of 30 ml. Cervical examination was performed by the obstetric staff who were not involved in this study in the delivery room hourly until cervix dilation reached 4.0 cm or more.

If an inadvertent dural puncture with the epidural needle during epidural catheterization was encountered, therapeutic procedures were followed (see Table 3, Supplemental Digital Content 3, which is a table listing possible therapeutic maneuvers after accidental dural puncture and the accidental rate in the current study, http://links.lww.com/ALN/A545). This population was treated on an intention-to-treat analysis.

Peripartum Management and Monitoring

A catheter was inserted in a right or left antecubital vein for fluid and drug administration. Ringer's solution (8 ml/kg) was titrated 15 min before initiation of the epidural analgesia. Intrapartum fluid management included replacement of preexisting fluid deficits, normal losses (maintenance requirements), quantification and measurement of urine, hemodynamic variables, and hemoglobin concentration.

The maternal parameters monitored during the whole study from before the analgesic procedures to the end of the labor included the heart rate by three-lead electrocardiograph, respiratory rate, noninvasive systolic and diastolic blood pressure, mean arterial pressure, and fingertip pulse oximetry.

If necessary, the intrauterine pressure sensor was placed to show the intensity of uterine contraction. Oxytocin was infused by the nursing staff set by the obstetricians according to the clinical guidelines. A decision whether an operative delivery was necessary was made by the obstetrical team that was not involved in the study depending on maternal and fetal indications. The treatment of obstetric staff was standardized according to the standard care procedures with or without EA.

The patient-derived VAS scores of pain with the 100-mm gauge (based on a 0–100 linear VAS: 0 = no pain, 100 = worst pain imaginable) were recorded at analgesia request, and were then measured hourly from the initiation of epidural analgesia to the completion of the labor. The average scoring of pain was calculated to each woman at the end of the labor. In addition, the maternal satisfaction with analgesia was assessed with the VAS system (a 0–100 linear VAS: 0 = dissatisfactory, 100 = very satisfactory). Finally, the incidence of the side effects, such as nausea, vomiting, pruritus, shivering, and urinary incontinence or retention throughout the study were recorded by the follow-up physicians according to the maternal reports; maternal oral temperature, hypotension and tachycardia were measured by caregiver intermittently (see Supplemental Digital Content 4, which is a table listing all side effects encountered after epidural analgesia, http://links.lww.com/ALN/A546).

Fetal and Neonatal Management

A continuous external electronic fetal heart-rate monitoring and tocodynamometry were made. Apgar scores were rated by the pediatric personnel according to the standard assessment. Umbilical-cord blood gas analysis was performed by the investigators.

Primary Outcome

The method of operative delivery, *i.e.*, the rate of CS was selected as the primary outcome of the different analgesic procedures.

Secondary Outcome

The following measures were selected as the secondary outcomes: the indication for Cesarean delivery; rate of instrument-assisted delivery; the time to vaginal delivery, latent phase, and active phase of the first stage and the second stage; the duration of epidural analgesia; the verbal ratings of VAS pain at the time of analgesic request and epidural placement; the subjects were also asked to rate their contraction pain at the endings of different phases of labor determined by cervical examination; satisfaction with analgesia after completion of vaginal delivery; oxytocin requirement; the maternal oral temperature; the incidence of side effects from epidural puncture and drug delivery.

In addition, we investigated the association between the maternal demographic variables and the rates of Cesarean delivery. Each one unit increase in age ($\Delta = 1$ yr), weight ($\Delta = 1$ kg), height ($\Delta = 1$ cm), and oxytocin use ($\Delta = 1$ mU/min) are assessed by using multivariate regression modeling.

Infant outcomes include the body weight, Apgar scorings, umbilical-cord blood gas measurement, antibiotic treatment, and sepsis assessment. Neonatal sepsis evaluation was performed as previously reported.[11] In brief, a blood culture and a complete blood count of the neonate suspected for sepsis possibility performed and followed by a lumbar puncture if one major or two minor criteria presented at the time of the study. Major criteria included rupture of membranes for more than 24 h or a sustained fetal heart rate of more than 160 beats per minute 15 min or longer. Minor criteria included a low-grade maternal temperature of 37.5°C to 38°C, rupture of membranes for 12 to 24 h, maternal admission white blood cell count of more than 15,000 cells/ml^3, or 5-min Apgar score less than 7.

Sample Size

A prestudy power table where δ (the mean difference in Cesarean delivery recorded in a pilot study, *i.e.*, a difference of 2.3% in the CS rate) equaled 19.1% in the latent phase analgesia group and 16.8% in the active phase analgesia group, two-sided $\alpha = 0.05$, one-sided $\beta = 0.10$, and the power of test = 0.90. Therefore, a minimal sample size of 5,840 subjects per group was needed to detect this difference. We increased the sample size to 7,500 in each group to account for potential missing data and dropouts during the 5-yr study course. The approximately 20% increase in sample size was mainly based on an institutional estimate that around 14% (median; interquartile range 8% to 22%) of patients dropped out or had missing data during the follow-up period in our previous clinical trials (the major reason for such a high dropout rate was because Chinese people had a different philosophical view about human research that differs from the Occidental population). In addition, given the long-lasting period of this study, during which many factors would have influenced subject enrollment, such as changes in patient's attitude and knowledge about epidural and clinical study, and increment of physician's experience, and improvement of medical facilities, etc., we increased the sample size to 7,500 per group using the upper limit 22%.

Statistical Analysis

All our data analyses, were first performed for patients in both of the intervention groups to which they were allocated – *i.e.*, on an intention-to-treat basis. Excluded and withdrawn subjects after randomization because of protocol violation and patient-controlled analgesia device were considered as the cases that encountered CS and analyzed in the group to which they were randomized according to the data that were available. In addition, the per protocol population analysis included all subjects who underwent the study intervention and completed the study. Excluded and withdrawn subjects, including protocol violation and patient-controlled analgesia device cases were excluded in this population. The primary analysis was based on the CS rate of both intention-to-treat and per-protocol populations.

Values are expressed as the mean, SD, median, interquartile range, or numbers. All categorical data were analyzed with a chi-square test to indicate the trend. The difference in parametric data, including the demographic data and background characteristics, were compared with Student *t* test. Mann–Whitney U test was used in analyzing nonnormally distributed variables and presented as the medians and interquartile ranges, including the effects of the epidural analgesia on patient's self-rated VAS scorings of pain and satisfaction, and in the duration of labor and each stage of delivery, oxytocin use, gestational age of fetus, and the highest sensory block level. Cumulative-event curves indicating different time lengths of labor were estimated with the Kaplan-Meier method, and the groups were compared using the log-rank test used elsewhere.[12]

Multivariable logistic regression analyses were performed to assess the adjusted association between maternal baseline variables and CS. First, a bivariate analysis was performed by using a liberal significance level of $P < 0.25$ to identify the baseline variables that were independently associated with the primary outcome for inclusion in the modeling after controlling for the other variables.[13] Modeling, was then performed by stepwise forward method with a criterion of $P < 0.05$ for variable retention in the models. In the logistic regression model, the independent variables assessed included age, height, weight, smoking status, and oxytocin infusion. Smoking status (0 = No; 1 = Yes) was entered as dichotomous variable for the logistic regression analysis. A Pearson correlation matrix of variables was used to identify collinear predictive variables.[13] Furthermore, Hosmer-Lemeshow test was used to assess the models' fit (larger

Table 1. Demographic and Background Characteristics of the Subjects*

Characteristic	Latent Phase Analgesia (n = 6,394)	Active Phase Analgesia (n = 6,399)	*P* Value
Age at delivery, yr	26.7 ± 4.8	27.0 ± 4.4	0.94
Weight, kg	79 ± 14	78 ± 16	0.93
Height, cm	161 ± 5	161 ± 7	1.0
Gestational age of fetus, wk			0.84
Median	40	40	
Interquartile range	39–40	39–40	
Current smoker, n (%)	1,071 (16.8)	1,122 (17.5)	0.24
Spontaneous rupture of membranes > 12 hr before oxytocin infusion, n (%)	921 (14.4)	957 (14.9)	0.38
Verbal ratings for pain intensity at analgesia request with VAS (0–100 mm)†			0.49
Median	66	74	
Interquartile range	43–86	40–89	
Vital signs before analgesia request			
Blood pressure			
Systolic pressure, mmHg	126 ± 12	123 ± 13	0.78
Diastolic pressure, mmHg	76 ± 6	75 ± 7	0.86
Heart rate, beats/min	73 ± 8	72 ± 8	0.89
Respiratory rate, breaths/min	21 ± 4	22 ± 3	0.75
Oral temperature, °C	37.2 ± 0.2	37.1 ± 0.3	0.66

* Plus-minus values indicate the means ± standard deviation (SD).

† Visual Analog Scale (VAS) of pain is a 100-point linear gauge in which 0 indicates no pain and 100 indicates worst pain imaginable.

P value means better fit or calibration), and predictive accuracy was assessed by the c-index as recommended elsewhere.[13,14] The odds ratio (OR) and its 95% confidence interval (95% CI) were calculated. The statistical significance was accepted at the level of $P \leq 0.05$.

Analyses were performed by using GraphPad Prism version 5.0 (GraphPad Software Inc., San Diego, CA) or SPSS version 13.0 (SPSS Inc., Chicago, IL).

Results

Fifteen thousand gravidas were screened (fig. 1). We excluded 2,207 subjects during the screening period because of the following reasons: 732 (33.2%) were without vertex presentation; 667 (30.2%) were diagnosed with diabetes and pregnancy-induced hypertension; 567 (25.7%) had twin gestation and breech presentation; 113 (5.1%) were not in the inclusion range of age (18 to 45 yr) at delivery; 87 (3.9%) were not willing to participate in the study; 30 (1.4%) were alcoholic; 11 (0.5%) had history of the use of centrally acting drugs. Finally, a total of 12,793 subjects were randomly assigned to the two groups and followed-up. After randomization, 164 subjects were excluded, and 6,274 subjects in the latent phase analgesia group and 6,355 subjects in the active phase analgesia group completed the whole study. Of the 164 excluded patients, 143 (87.2%) were excluded because of violation of the study protocol during data collection, and 21 subjects were excluded because of issues of the patient-controlled analgesic device and accidental dural puncture. The reasons for the protocol violation for the excluded 143 subjects was as follows: in 102 subjects whose cervix were over 4.0 cm were randomly assigned into the latent phase analgesia group; the cervical diameter was less than 4.0 cm or without cervical examination and then epidural analgesia was initiated in the active phase group (28 women), and 13 parturients whose cervix were less than 4.0 cm refused meperidine and received epidural analgesia in this group. All these excluded patients after randomization were treated as the intention-to-treat analysis.

Table 1 summarizes the demographic, background characteristics, and baseline vital signs (all were within the physiologic ranges). No significant difference was observed between the two groups.

The rate of Cesarean delivery in both groups displayed no statistically significant difference, $P = 0.51$. In addition, no significant differences were observed between the two groups in the indications of Cesarean delivery, the percentages of subjects who were treated with oxytocin infusion, or the maximal oxytocin dose. There was also no statistical significance in the rate of instrument-assisted delivery, $P = 0.10$ (table 2). Besides, similar results received when analyzing the primary outcome on the per protocol population basis, and there were no significant differences in the CS rate and instrument-assisted deliveries, $P = 0.86$ and 0.91, respectively.

There were no significant differences in the length of labor before vaginal delivery, the time to latent and active phases in the first stage, and the duration of the second stage of the labor between the two groups (table 2). Figure 2 presented the time durations of different labor stages in Kaplan-Meier curves, and there was no difference in the median time from the request for analgesia and complete cervical dilation (562 min *vs.* 554 min in the latent and active phase groups, respectively; $P = 0.42$; fig. 2A), the time to the vaginal delivery (627 min *vs.* 661 min in the latent and active phase groups,

Table 2. Major Maternal Outcomes after Epidural Analgesia*

Outcomes	Latent Phase Analgesia (n = 6,394)	Active Phase Analgesia (n = 6,399)	*P* Value
Method of delivery			
Cesarean, n (%, 95% CI)	1,486 (23.2, 18.7–24.5)	1,456 (22.8, 18.7–24.9)	0.51
Instrument-assisted vaginal, n (%, 95% CI)†	753 (11.8, 10.5–14.2)	814 (12.7, 10.3–13.5)	0.10
Indications for cesarean‡			
Arrest of dilation, n (%)	979 (65.9)	935 (64.2)	0.34
Arrest of descent, n (%)	214 (14.4)	205 (14.1)	0.80
Other fetal status, n (%)	293 (19.7)	316 (21.7)	0.18
Other outcomes			
Average cervical dilation before epidural placement, cm			< 0.0001
Median	1.6	5.1	
IQR	1.1–2.8	4.2–5.7	
Length of labor (from analgesia request to vaginal delivery), h§	11.3 ± 4.5	11.8 ± 4.9	0.90
Duration of first stage, min			
Latent phase	479 ± 52	485 ± 58	0.22
Active phase	111 ± 44	128 ± 50	0.68
Duration of second stage, min	63 ± 35	67 ± 36	0.87
Average VAS pain ratings (0 – 100 'mm)‖			
First stage of labor			
Latent phase			0.18#
Median	32	48	
IQR	26–40	33–65	
Active phase			0.80#
Median	28	25	
IQR	20–40	20–45	
Second stage of labor			0.46#
Median	22	20	
IQR	12–36	15–40	
Use of oxytocin after analgesia, n (%)	1,492 (23.3)	1,518 (23.7)	0.60
Meperidine consumption, mg	50 ± 25	75 ± 50	0.48
Maximal oxytocin dose, mU/min			0.07#
Median	15	13	
IQR	10–23	9–20	
Duration of epidural analgesia, h			0.02#
Median	12.6	4.8	
IQR	9.7–17.5	3.1–6.4	
Highest sensory block	T8 (T6–T9)	T8 (T6–T9)	1.0#
Oral temperature during labor, °C	37.4 ± 0.4	37.2 ± 0.3	0.52
Breastfeeding success at 6 weeks, n (%)	4,485 (70.1)	4,977 (77.8)	< 0.0001
Maternal overall satisfaction score with analgesia (VAS, 0 – 100 mm)			0.01#
Median	84	62	
IQR	65–95	50–75	

* Plus-minus values are means ± standard deviation (SD); † the percentage was calculated with the number of subjects need instrumental delivery to the total number of participants precluded to the Cesarean-delivered ones; ‡ the percentage was calculated with the number of subjects indicating to need Cesarean section to the total number of participants had Cesarean delivery; § the length of labor indicates the time period from the onset of regular uterine contraction to the time after delivery of placenta; ‖ the VAS system of pain or satisfaction rating with analgesia is a 0- to 100-mm linear gauge in which 0 indicates no pain or dissatisfaction with analgesia and 100 indicates worst pain imaginable or very satisfactory with analgesia; # non-normally distributed data were presented as the medians and interquartile ranges, and corresponding *P* values were calculated with the Mann-Whitney U test. If not indicated, the *P* values were calculated by the chi-square test for categorical data.

VAS = Visual Analog Scale; IQR = interquartile range.

respectively; $P = 0.08$; fig. 2B), the time to latent and active phases of first stage (fig. 2C and D), the time to second stage (fig. 2E), and the time to Cesarean and instrumental deliveries (fig. 2F and G).

The average VAS ratings of pain at analgesia request were similar in both groups (table 1). There were no statistically significant differences in the VAS pain scorings during the latent and active phases and the second stage of labor (table 2). The duration of epidural analgesia in both groups was calculated from the bolus injection of the drug mixture into epidural space to the disappearance of the sensory block. The analgesic time epidurally in the latent phase group was much longer (median 12.6 h) *versus* the active phase group (median 4.8 h), $P = 0.02$.

The intrapartum nausea and vomiting had a significantly lower incidence in the latent phase analgesia group than the active phase analgesia group. Fewer patients experienced pruritus in the active phase analgesia group. No significant difference was observed in the other side effects (high temperature greater than 38°C, urinary incontinence and retention, shivering, and

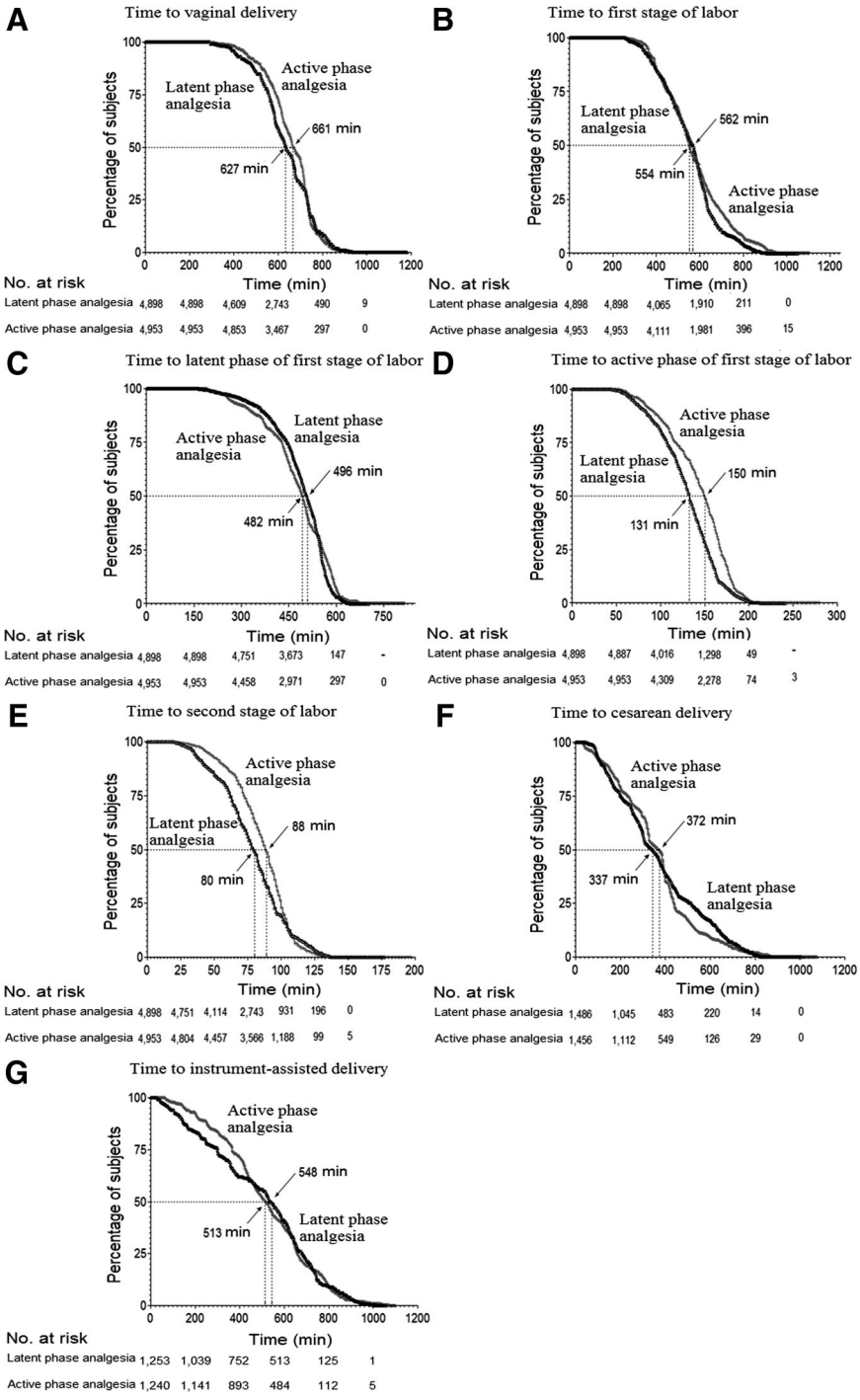

Fig. 2. Kaplan-Meier curves for the length of labor. *Arrows* indicate median values of time. (*A*) Time to successful vaginal delivery. The difference in both of the median time to delivery was –34 min (95% CI, –58 to –12 min, $P = 0.35$). (*B*) The merged time to latent and active phase of the first stage of labor. The difference in both of the median time was –8 min (95% CI, –13 to –3 min, $P = 0.84$). (*C*) Time to latent phase of first stage of labor. The difference in both of the median time was –14 min (95% CI, –22 to –4 min, $P = 0.67$). (*D*) Time to active phase of first stage of labor. The difference in both of the median time was –19 min (95% CI, –37 to –8 min, $P = 0.39$). (*A to D*) Time 0 is the time of the analgesia request. (*E*) Time to the second stage of labor. The difference in the median time was –8 min (95% CI, –18 to –2 min, $P = 0.92$). (*F*) Time to delivery by Cesarean section. The difference in the median time was –35 min (95% CI, –55 to –20 min, $P = 0.44$). (*G*) Time to instrument-assisted delivery. The difference in the median time was –35 min (95% CI, –46 to –23 min, $P = 0.53$).

hypotension) between the two groups (see Table 4, Supplemental Digital Content 4, which is a table listing all side effects encountered after epidural analgesia, http://links.lww.com/ALN/A546). The breastfeeding success at 6 weeks after delivery was less in the latent phase analgesia group compared with the active phase analgesia one, $P < 0.0001$ (table 2). There was no statistically significant difference in the neonatal outcomes between groups (table 3).

Table 4 summarizes the association between the maternal demographic variables and the rates of Cesarean delivery analyzed with a multivariate regression. Each one unit increase in age (yr), weight (kg), height (cm), and oxytocin use (mU/min) are associated with Cesarean delivery (the adjusted OR were 1.46, 1.67, 1.25, and 2.20, respectively, all $P < 0.05$), but current smoking status was not.

Discussion

The data from this 5-yr study demonstrate that providing epidural analgesia in the latent phase of spontaneous

Table 3. Infant Outcomes after Epidural Analgesia*

Outcomes	Latent Phase Analgesia (n = 6,394)	Active Phase Analgesia (n = 6,399)	*P* Value
Weight, g	3,562 ± 454	3,488 ± 471	0.85
1-min Apgar < 7, n (%)	879 (13.7)	912 (14.2)	0.41
5-min Apgar < 7, n (%)	46 (0.7)	53 (0.8)	0.48
Umbilical cord gases measured, n (%)	5,545 (86.7)	5,590 (87.3)	0.28
Umbilical vein pH	7.30 ± 0.05	7.30 ± 0.06	1.0
Umbilical artery pH	7.21 ± 0.06	7.22 ± 0.08	0.87
Low umbilical cord pH (artery < 7.20), n (%)	1,462 (22.9)	1,516 (23.7)	0.27
Neonatal sepsis evaluation, n (%)	132 (2.1)	157 (2.4)	0.14
Neonatal antibiotic treatment, n (%)	836 (13.1)	861 (13.4)	0.52

* Plus-minus values are means ± standard deviation (SD).

labor at term, compared with the active phase, did not increase the rate of intrapartum Cesarean delivery. In addition, no association was found between early epidural analgesic intervention and the rate of operative vaginal delivery.

These results have extended the findings from other studies. Wong *et al.* have compared the risk of Cesarean delivery after early neuraxial analgesia (combined spinal-epidural analgesia, but not EA) and systemic analgesia when the cervix was between 2 and 4 cm, in which the cervical dilation reached at least 2.0 cm.[3] Chestnut's studies evaluated early epidural analgesia at the cervical dilation was at least 3.0 cm or greater.[15,16] Ohel reported an approximately 10% CS rate in both groups when an epidural was placed at a mean cervical dilation approximately 2.4 cm *versus* 4.6 cm, which was enviable but may lack generalizability to other clinical environments.[4] In the current study, we performed epidural analgesia in the latent phase of the first stage of labor at the cervical dilation of at least 1.0 cm *versus* the active phase analgesia at 4.0 cm or more, and no statistical difference in CS rate was found. As such, the interventional window of labor analgesia can be enlarged from 4.0 cm to 1.0 cm of cervical dilation.

Wong *et al.* found that intrathecal (spinal) opioid use significantly shortened the first stage of labor compared with the systemic opioid administration.[3] In the current trial, we detected a slightly longer but not statistically significant prolonged duration of the first stage of labor in women who received epidurals in the latent phase. As such, we can still conclude that the earlier initiation of epidural analgesia in nulliparous women does not prolong the progress of labor.

The rate of instrument-assisted delivery might be increased if the epidural infusion of local anesthetics lasted longer,[17,18] but our data did not support such demonstration. In our study, the median time of instrumental delivery was similar in both of the groups (548 min *vs.* 513 min in the latent and active phase analgesia women, respectively). Meanwhile, the percentages of instrumental delivery in both groups were nearly same (approximately 12.0%). Therefore, epidural analgesia in early labor does not also increase the rate of instrument-assisted delivery.

Gambling *et al.* reported an association between epidural analgesia and intrapartum oxytocin infusion,[19] and other studies have found that epidural analgesia combined with low-dose oxytocin infusion would increase the rate of Cesarean delivery.[20] In contrast to these studies, we did not find significant association among epidural analgesia, oxytocin requirement, and maternal delivering outcomes, which was in agreement with the results of Wong *et al.*[3]

In our study, we used meperidine as the rescue analgesic until the cervix dilated adequately to perform epidural analgesia in both groups. We did not find significant difference in the VAS pain ratings in both groups during latent labor, although epidural analgesia was given in the latent phase group, but meperidine in the active phase women. Jain *et al.* reported that women who received meperidine still felt moderate pain (VAS 40–69 mm),[21] and the median VAS score in another study lowered significantly 30 min after the meperidine to 54 mm compared with the saline control at 78 mm.[22] Our finding was consistent with these data that meperidine during latent labor in the active phase analgesia

Table 4. Logistic Regression to Evaluate the Association between Maternal Demographic Variables and Cesarean Delivery

Variable	Coefficient	Standard Error	Simple OR (95% CI)	*P*	Adjusted OR (95% CI)*	*P* Value
Age (each 1-yr increase)	0.69	0.52	1.39 (1.06–3.25)	0.007	1.46 (1.11–3.64)	0.016
Height (each 1-cm increase)	0.54	0.42	1.16 (1.02–2.18)	0.021	1.25 (1.08–2.47)	0.039
Weight (each 1–kg increase)	0.93	0.57	1.61 (1.34–4.01)	< 0.001	1.67 (1.42–4.35)	0.004
Current smoker†	–0.23	0.44	0.81 (0.72–1.37)	0.78	0.86 (0.80–1.52)	0.83
Oxytocin (each increase by 1 mU/min)	1.01	0.65	2.01 (1.78–5.12)	< 0.001	2.20 (1.83–5.56)	0.006

* Odds ratios are adjusted for other terms included in the model; † smoking status was calculated by referring to "No smoker" as the reference.

group produced moderate pain-relieving effect with the median VAS score 48 mm.

We measured the oral temperature during epidural analgesia recommended by Banerjee *et al.* that oral temperature is a preferred routine detection of maternal pyrexia in labor for its positive correlation with intrauterine temperature.[23] However, the 0.2ºC difference in oral temperature that we detected was so small as to be irrelevant in the clinical environment despite the statistical difference that was detected. We did not detect a significant increase in temperature of the magnitude that was shown by Camann *et al.*[24]

Nausea and vomiting are common side effects induced by pregnancy.[25] In addition, pain is a major cause of nausea.[26] We found that effective epidural analgesia in early labor can decrease intrapartum nausea and vomiting more significantly than the later labor analgesia. Also, opioids are a common cause of nausea, so the fact that our active labor patients got more meperidine likely played a role. Our data evidenced that the longer the time to epidural analgesia, the more the incidence of pruritus during labor. This is mainly because longer epidural analgesia means a relatively larger dose of lipophilic opioid was absorbed into blood, which produced more incidence of itching.

We have found potentially controversial results with respect to the influence of intrapartum labor pain control on postpartum breastfeeding initiation. Chang and Heaman found in their cohort study that epidural analgesia did not inhibit effective breastfeeding.[27] However, the Academy of Breastfeeding Medicine Protocol Committee considered that epidural analgesia with narcotic during labor has adverse effect on breastfeeding by delaying early skin-to-skin contact between mother and baby.[28] In addition, Volmanen's questionnaire survey found the problem of "not having enough milk" was more often reported by those who had received epidural analgesia.[29] In our study, more than 70% of women in both epidural groups had successful breastfeeding, but the active phase analgesia group had more successful cases in breastfeeding than the latent phase analgesia group, which is consistent with previous reports that epidural analgesia is associated with impaired spontaneous breastfeeding, including breastfeeding at discharge from the hospital.[30–32] This difference is likely to be associated with a relatively longer duration of analgesia in the latent phase group compared with the active phase analgesia women, although the precise mechanism underlying such phenomenon is yet to be guaranteed in the future research.

The 1-min and 5-min Apgar scores were similar in both of the groups. This expressed early epidural analgesia does not exert significant influence on neonatal Apgar ratings. The results of umbilical-cord blood gases measurement were not different in agreement with the data from Wong *et al.*[3] Goetzl *et al.* found that epidural analgesia could increase the rate of neonatal sepsis work-ups in afebrile women, in which the rate was 20.4%.[11] Nonetheless, we did not find convincing evidence that epidural analgesia performed early or late in spontaneous labor increases the rate of neonatal sepsis. The 0.2ºC difference in maternal oral temperature in our study was not merely statistically nonsignificant, but it was not associated with an increase in neonatal sepsis work-ups. According to the report of Fisler *et al.*, neonates received more diagnostic tests and therapeutic interventions such as antibiotic administration in those whose mothers received epidural analgesia for pain relief during labor than infants born after an elective Cesarean section.[33] The neonatal antibiotic treatment in the current study was identical (approximately 13%) in both groups and in agreement with the aforementioned report (approximately 10–14%).

We also analyzed the association between maternal demographic variables and CS rate. In agreement with other previous studies,[3,34] our results showed that each one-unit increase in age, weight, height, and oxytocin infusion are significantly associated with the increase of Cesarean delivery. Nevertheless, the current smoking status did not increase CS rate. These indicate that maternal baseline characteristics are relatively more important predictors for Cesarean delivery than the intrapartum epidural analgesia intervention.

This study was subject to several limitations. First, this study lasted 5 yr; for such a long enrollment period, any changes in healthcare made may have influenced the results. The experience and knowledge of caregivers and the medical instruments were improved, and the guidelines for parturient care were perfected, and the increasing recognition for better medical service of parturients all were potential confounders for the difference detection of CS rate. In addition, we merely investigated the nulliparous women with single and vertex presentation, but whether such results could be applied to other populations is not known. Another question is the difficulty in blinding the study treatment groups from the obstetricians who ultimately made the decision for Cesarean delivery. Finally, we monitored the fetal heart-rate as a possible indicator for emergency Cesarean delivery, although the association among epidural analgesia, fetal heart-rate variability, and Cesarean delivery was not analyzed. In our study, the occurrence of an unfavorable fetal heart rate in both of the groups are similar (data are not shown).

In summary, this study provides robust evidence that epidural analgesia in the latent phase (at the cervical dilation of at least 1.0 cm) of the first stage of spontaneous labor at term does not prolong the progression of labor and not increase the rate of Cesarean section in nulliparous women compared with the active phase analgesia at the cervical dilation 4.0 cm or greater.

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