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Patient-requested Neuraxial Analgesia for Labor

Impact on Rates of Cesarean and Instrumental Vaginal Delivery

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A systematic review, including a meta-analysis, on the timing effects of neuraxial analgesia (NA) on cesarean and instrumental vaginal deliveries in nulliparous women was conducted. Of 20 articles identified, 9 met the inclusion quality criteria (3,320 participants). Cesarean delivery (odds ratio, 1.00; 95% confidence interval, 0.82–1.23) and instrumental vaginal delivery (odds ratio, 1.00; 95% confidence interval, 0.83–1.21) rates were similar in the early NA and control groups. Neonates of women with early NA had a higher umbilical artery pH and received less naloxone. In the early NA group, fewer women were not compliant with assigned treatment and crossed over to the control group. Women receiving early NA for pain relief are not at increased risk of operative delivery, whereas those receiving early parenteral opioid and late epidural analgesia present a higher risk of instrumental vaginal delivery for nonreassuring fetal status, worse indices of neonatal wellness, and a lower quality of maternal analgesia.

THE American Society of Anesthesiologists and the American College of Obstetricians and Gynecologists (ACOG) have produced a joint statement#[1] asserting that maternal request is a sufficient medical indication for pain relief during labor, and that pain management should be provided whenever medically indicated. Neuraxial analgesia (NA) is the only available consistently effective technique of pain control during labor and delivery.[2–4] In North America and Western Europe,[5,6] pregnant women with painful labor request most frequently NA.

American Society of Anesthesiologists and ACOG evidence-based practice guidelines[7,8] are useful for making decisions to improve obstetric care outcome, but the topic of NA timing is still controversial. The current Practice Guidelines of the American Society of Anesthesiologists[7] state that cervical dilation is not a reliable means of determining when regional analgesia should be initiated, and that regional analgesia should be administered on an individualized basis. This position is supported by randomized controlled trials (RCTs)[9–11] in which NA timing was the primary independent variable of analysis and no association between early NA administration and operative delivery was found. However, these RCTs were small and with high crossover rates.[9–11] The current ACOG Practice Bulletin[8] states that, when feasible, obstetric practitioners should delay the administration of NA in nulliparous women until cervical dilation reaches 4–5 cm, and other forms of analgesia should be used until that time. This recommendation is tempered by the statement that women in labor should not be required to reach an arbitrary cervical dilation. ACOG clinical guidelines are sustained by observational and randomized controlled studies[12–14] in which early NA was associated with an increased risk for cesarean delivery (CD). However, this association was an observation[12] or the result of a secondary analysis of RCT data.[13,14] Therefore, both practice guidelines on this topic are based primarily on consensus and expert opinion, and in a recent review the lack of consistent evidence has been reaffirmed.[15] In June 2006, ACOG has updated its position by a new report of consensus and expert opinion,[16] stating that, when compared with intravenous systemic analgesia, the initiation of early NA does not increase the risk of CD.

The main objective of this investigation is to perform a systematic review of the effects of NA timing in nulliparous women on CD and instrumental vaginal delivery (IVD) as primary outcomes, and on neonatal parameters related to newborn wellness as secondary outcomes.

Materials and Methods

Searching, Selection, and Validity Assessment

We sought RCTs and cohort studies (CSs), either as full text or in abstract form, about the effects of NA timing on obstetric outcomes. We included abstracts in the attempt to search all available data with the aim of reducing publication bias.[17] Articles were retrieved from

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American Society of Anesthesiologists, House of Delegates: Statement on pain relief during labor. October 1999. Available at: http://www.asahq.org/publicationsAndServices/standards/32.html. Accessed February 2, 2006.

the Cochrane Library (January 2006), EMBASE, and MEDLINE (January 1990 to June 2006) databases using the following terms as medical subject headings, text, and key words, both stand-alone or in combination: *epidural* and *combined spinal–epidural analgesia*; *labor first stage* and *labor onset*; *instrumental vaginal delivery* and *cesarean delivery*. We identified additional studies in the reference lists of previously published reviews and retrieved articles, and we hand-searched for other data sources in the annual proceedings (2000–2005) of the Society for Obstetric Anesthesia and Perinatology and the ACOG. Publication language was not a search criterion.

We selected studies on the effects of early NA (defined as epidural or combined spinal–epidural analgesia initiated before the cervix is dilated to 4–5 cm) on obstetric outcomes. Studies that defined "early labor" relative to fetal station were excluded. We identified quality studies adopting the three-pronged restriction criteria proposed by Vandenbroucke,[18] based on research topic, study design, and analysis. Therefore, studies were selected according to the following inclusion criteria: (1) effects of early NA administration on obstetric outcomes as main research topic; (2) nulliparous women requiring labor pain relief as participants of the study design; and (3) comparison of early NA *versus* early parenteral opioid, or late epidural analgesia (EA), or both early parenteral opioid and late EA (control group) in laboring women as group analysis. Studies in which the analysis was performed by stratifying according to the degree of cervical dilation and/or with adjustment for potential confounders were excluded.

Randomized controlled trials were also evaluated according to the criteria proposed by Jadad *et al.*[19] The Jadad validated scale is based on three items (randomization, blindness, and description of withdrawals and dropouts) and has a maximum score of five points, assigned on the basis of the quality of randomization and blinding method (absent or inappropriate = 0, appropriate but not described = 1, appropriate and described = 2) and of the outcome report of all enrolled subjects (not described = 0, described = 1).

The Vandenbroucke criteria and Jadad scoring system were independently evaluated by two investigators (M.M., G.P.), and when evaluation or score differed, the study was further assessed to reach consensus.

Data Abstraction and Study Characteristics

Data were independently collected by two investigators (M.M, G.P.), with any discrepancy resolved by reinspection of the original article. To avoid transcription errors, the data were input into statistical software and rechecked by different investigators (G.C., N.B.).

We analyzed RCTs and quality CSs on the effects of early on-demand EA or combined spinal–epidural analgesia on mode of delivery in nulliparous women. To better define each study, the following pieces of information were retrieved: sample characteristics (race, prenatal education, age, weight, height, gestational age, premature or spontaneous rupture of membrane, and pregnancy-associated disease), details of obstetric care (induced labor, amniotomy, oxytocin augmentation and dose, and labor management protocol), anesthetic interventions (pre-NA fluid loading, mode and dose of analgesia), and neonatal interventions (whether naloxone was administered to the infant). For each RCT, we searched for information on withdrawals and dropouts of enrolled laboring women, resulting in their exclusion from the analysis. In addition, we noted noncompliance and crossover of the patients who were originally included in the studies.

Primary outcomes were the CD and IVD rates. Secondary outcomes were neonatal weight, incidence of neonatal Apgar score less than 7 at 1 and 5 min, neonatal umbilical arterial pH (UApH) and venous pH (UVpH), and naloxone use. All outcome measurements were clearly and consistently defined.

The analysis was also performed on other maternal outcomes such as oxytocin use and labor duration. The latter was divided into two stages: from time 0 to full cervical dilation (first stage), and from full cervical dilation to delivery (second stage). In the selected studies, time 0 was defined as time of randomization,[9,10,20] time of admission to the delivery room,[11] time of diagnosis of "true" labor,[21] time of initiation of analgesia,[22] and time corresponding to 4 cm of cervical dilation.[23] Duration of labor was reported as mean in five studies[9–11,20,21] and as median in two studies.[22,23] Methodologic details such as noncompliance with the assigned protocol and crossover to other treatment, used as surrogate outcomes for maternal satisfaction and analgesia effectiveness, were also analyzed.

Quantitative Data Synthesis

To reach a high statistical power while maintaining a low systematic error, we performed a meta-analysis of RCTs and quality CSs. Meta-analytic techniques (analysis software RevMan, version 4.2; Cochrane Collaboration, Oxford, England, United Kingdom) were used to combine studies using odds ratio (OR) and 95% confidence interval (CI) for dichotomous variables, and weighted mean difference and 95% CI for continuous variables. A statistical difference between groups was considered to occur if the pooled 95% CI did not include 1 for the OR or 0 for the weighted mean difference. An OR of less than 1 or a negative weighted mean difference favored early NA when compared with the control group. Two-sided *P* values were calculated. A random-effects model was used for all analyses.[24] Heterogeneity was assessed by using the Q and I^2 tests.[25,26] When the Q test *P* value was less than 0.05 and/or the I^2 was greater than 25%, heterogeneity was considered significant, and the

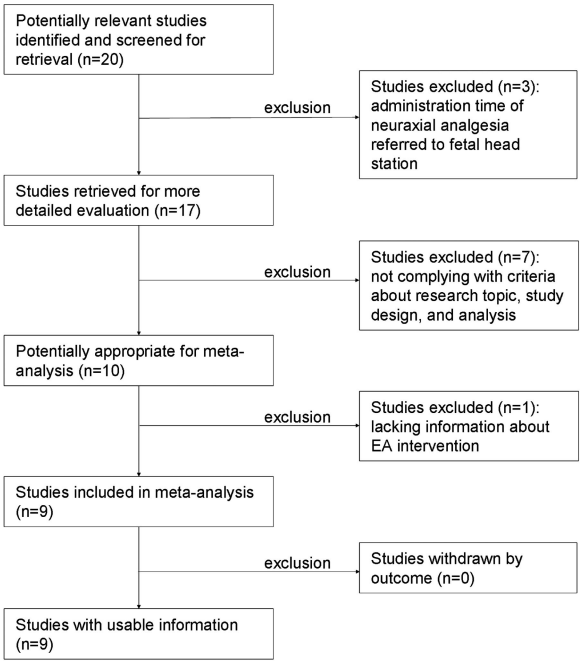

Fig. 1. Flowchart summarizing the studies selection procedure for the meta-analysis. EA = epidural analgesia.

pooled results were recalculated by excluding heterogeneous studies. If only one study was heterogeneous, it was reported when its sample was larger than pooled included studies. If more than one study was heterogeneous, they were pooled together, and their results were reported only if homogeneous.

The definition of duration of first stage of labor varied from study to study. Therefore, to pool data with different time 0, duration ratio (99% CI) was used and calculated as follows[27]:

$$\text{Duration ratio} = \frac{\text{Early NA labor duration, first stage (min)}}{\text{Control labor duration, first stage (min)}}$$

Pooled result expresses the fraction (or percentage) of the increase or decrease of the first-stage labor duration of early NA with respect to control.

In addition, we performed two subgroup analyses on the basis of the study design (RCTs and quality CSs) for the main outcomes (CD and IVD), and two sensitivity analyses for CD and IVD indications (nonreassuring fetal status [NRFS] and dystocia).

Results

Trial Flow and Study Characteristics

We identified a pool of 20 published articles, 18 obtained by electronic database search and 2 abstracts found by means of manual searches (fig. 1). Three articles[28–30] were eliminated because the NA administration timing was related to fetal station. Another 7 articles[12–14,31–34] were excluded because they did not comply with one or more Vandenbroucke criteria.[18] Another article[35] was rejected because no detail on NA intervention was reported. Reasons for exclusion are reported in table 1. Therefore, 9 articles[9–11,20–23,36,37] meeting all of the inclusion criteria were selected: 5 RCTs, 1 impact CS, and 3 retrospective CSs (including 1 abstract). These studies involved a grand total of 3,320 patients and were all published in English. The studies were performed either in the United States[9,10,21–23,37] or in Israel,[11,20,36] from 1994 to 2006. Regarding the retrospective CS available only in abstract form,[37] only the comparison between early EA *versus* early parenteral opioid control groups (cervical dilation < 3 cm) was included (table 1); some print errors were clarified by checking the 2003 conference report of the Society for Obstetric Anesthesia and Perinatology,** and details of the population characteristics and interventions were obtained from another article[38] enrolling the same participants. Dr. Wong sent us additional unpublished data about her RCT,[22] regarding the mean and the SD of first- and second-stage labor duration, and the number of neonates receiving naloxone (Cynthia A. Wong, M.D., Associate Professor, Department of Anesthesiology, Northwestern University, Feinberg School of Medicine, Chicago, Illinois, written communication, January 17 and April 6, 2006).

All selected articles were concerned mainly with the effects of NA timing on obstetric outcomes and had a population sample of nulliparous women at term (> 36 weeks) with singleton fetus; only one CS had a mixed-parity sample, but reported the outcome of nulliparous women separately.[36] All studies enrolled women with uncomplicated pregnancies, except for the abstract,[37] which included a subgroup of women with pregnancy-induced hypertension. Two RCTs included women with induced labor.[9,20] All of the studies compared laboring women with early NA administration *versus* those who received early parenteral opioid, or late EA, or both early parenteral opioid and late EA (control group). Early NA groups had patients requesting initiation of EA in latent and early active phase of labor, defined as cervical dilation of 4 cm or less.[39] In one RCT,[11] the patients randomly assigned to the control group did not receive any intervention for pain relief before EA administration; moreover, no patient from either group received any intervention for pain relief after full cervical dilation.

All studies reported main obstetric outcomes. All studies but one[36] had data on CD rate, and all studies but one[37] reported data on IVD rate. Indications for CD and IVD were presented only in RCTs, and included dystocia and NRFS. Definitions of dystocia and NRFS were in accordance with the specific criteria of obstetric man-

** Camann WR: Conference report: Highlights of the 35th Annual Meeting of the Society for Obstetric Anesthesia and Perinatology, May 14–17, 2003; Phoenix, Arizona, US. Available at: http://www.medscape.com/viewarticle/456179. Accessed January 15, 2006.

Table 1. Inclusion and Validity Assessment of the Analyzed Studies

Authors, Year, Country	Study Design	Quality Assessment: Compliance with Three-pronged Restrictions (Y/N)	Quality Assessment: Jadad Scale	Included (Y/N)	Notes/Reason for Exclusion
Chestnut *et al.*,[9] 1994, United States	RCT	Y	3	Y	Healthy nulliparous women; induced labor included; 35% (26/75) in the control group received EA before cervical dilation of 5 cm
Chestnut *et al.*,[10] 1994, United States	RCT	Y	3	Y	Healthy nulliparous women; 15% (24/162) in the control group received EA before cervical dilation of 5 cm
Luxman *et al.*,[11] 1998, Israel	RCT	Y	2	Y	Nulliparous women; the control group did not receive any form of analgesia until a cervical dilation of 4 cm; both groups did not receive further EA boluses after full dilation; no statement on withdrawals and dropouts
Ohel and Harats,[36] 1994, Israel	rCS	Y	—	Y	Mixed-parity women with uncomplicated pregnancy; separate data for nulliparous women available
Ohel *et al.*,[20] 2006, Israel	RCT	Y	3	Y	Nulliparous women; induced labor included; intention to treat analysis
Rogers *et al.*,[21] 1999, United States	rCS	Y	—	Y	Healthy nulliparous women
Sharma *et al.*,[37] 2003, United States	rCS abstract	Y	—	Y	Nulliparous women; includes women with pregnancy-induced hypertension; two control groups: early parenteral opioid and late EA (the latter control group was excluded from meta-analysis because obtained by stratifying for the degree of cervical dilation)
Vahratian *et al.*,[23] 2004, United States	iCS	Y	—	Y	Nulliparous women; 2% (4/223) in early parenteral opioid group received EA; 8% (22/278) in early EA group received parenteral opioid
Wong *et al.*,[22] 2005, United States	RCT	Y	3	Y	Healthy nulliparous women; intention-to-treat analysis; 3% (11/362) in the control group received EA before cervical dilation of 4 cm
Hasling *et al.*,[28] 2001, United States	rCS abstract	Not evaluated	—	N	Nulliparous women; EA timing based on fetal head station.
Holt *et al.*,[31] 1999, United States	pCS	N	—	N	Mixed-parity women; compares fetal head station and cervical dilation at the time of EA placement for predicting cesarean delivery risk; analysis by multiple logistic regression
Lieberman *et al.*,[12] 1996, United States	rCS	N	—	N	Nulliparous women; the primary endpoint was to quantify the risk of cesarean delivery associated with EA; analysis was adjusted for confounding factors
Nageotte *et al.*,[14] 1997, United States	RCT	N	Not assessed	N	Nulliparous women; the primary endpoint was to study the association of CSE and EA with dystocia; EA timing analysis was *post hoc*
Robinson *et al.*,[29] 1996, United States	rCS	Not evaluated	—	N	Mixed-parity women; EA timing based on fetal head station
Seyb *et al.*,[32] 1999, United States	rCS	N	—	N	Nulliparous women; the primary endpoint was to quantify the risk of cesarean delivery associated with elective induction of labor; EA timing analysis by stepwise logistic regression
Sheiner *et al.*,[30] 1999, Israel	pCS	Not evaluated	—	N	Mixed-parity women; EA timing based on fetal head station
Thorp *et al.*,[33] 1991, United States	rCS	N	—	N	Nulliparous women; the control group was composed by patients not requiring pain relief
Thorp *et al.*,[13] 1993, United States	RCT	N	Not assessed	N	Nulliparous women with uncomplicated pregnancy; the primary endpoint was to determine the effect of EA on labor and delivery; EA timing is analyzed in a retrospective subgroup approach
Traynor *et al.*,[34] 2000, United States	rCS	N	—	N	Nulliparous women; aim: to quantify the association of cesarean delivery and EA management (EA timing included); multivariate analysis by stepwise logistic regression
Walker and O'Brien,[35] 1999, Canada	rCS	Y	—	N	Primiparous women; insufficient details about EA intervention

CSE = combined spinal–epidural analgesia; EA = epidural analgesia; iCS = impact cohort study; pCS = prospective cohort study; rCS = retrospective cohort study; RCT = randomized controlled trial.

agement and the interpretation of fetal heart rate (FHR) tracing adopted by each medical team (table 2).

Quantitative Data Synthesis

Overall rates of CD (OR, 1.00; 95% CI, 0.82–1.23; 8 studies, 2,980 participants) and IVD (OR, 1.00; 95% CI, 0.83–1.21; 8 studies, 2,816 participants) were similar in the early NA and control groups (figs. 2 and 3). No statistical heterogeneity among studies was detected (CD: Q statistic $P = 0.78$, $I^2 = 0\%$; IVD: Q statistic $P = 0.56$, $I^2 = 0\%$). In the RCT and quality CS subgroup analyses, no significant difference in CD and IVD between early NA and control groups was found (table 3). Sensitivity analyses for CD and IVD indications showed a significantly higher risk of IVDs for NRFS in parturient women with early parenteral opioid and late EA administration.

No significant difference between early NA and control groups was found in neonatal weight and Apgar scores less than 7 at both 1 and 5 min. Because the heterogeneity of Apgar score less than 7 at 1 min was significant (Q statistic $P = 0.11$, $I^2 = 55.2\%$), the pooled result was recalculated by excluding the heterogeneous study.[22] Excluding the heterogeneous trial (OR, 0.63; 95% CI, 0.44–0.91; 728 participants; $P = 0.01$),[22] no significant difference was observed (table 3). A significant difference favoring the early NA group was observed in neonatal UApH. No difference was found for UVpH, although heterogeneity was significant (Q statistic $P = 0.02$, $I^2 = 73.3\%$). Excluding the heterogeneous trial (weighted mean difference, 0.00; 95% CI, −0.01 to 0.01; 655 participants; $P = 0.99$),[22] a significant difference favoring the early NA group was detected for UVpH (table 3). Naloxone administration was significantly more frequent in newborns of women not receiving early NA (table 3).

First-stage labor duration (evaluated by the surrogate outcome duration ratio) and second-stage duration were not different. Regarding first-stage labor duration ratio, after exclusion of two studies[21,22] because of heterogeneity, the absence of difference was confirmed. Moreover, neither oxytocin use (overall and after randomization/analgesia) nor prenatal education was significantly different between groups (table 3).

Women receiving early NA were more compliant with the assigned treatment than those receiving control analgesia. Because heterogeneity was significant (Q statistic $P = 0.01$, $I^2 = 71.8\%$), the analysis was performed after excluding heterogeneous RCTs[9,10] and RCT with not estimable OR (all women compliant).[11] The pooled analysis of remaining studies (as well as the analysis of excluded studies) confirmed a significant difference between groups (table 3). Much fewer laboring women crossed over from the early NA to the control group than *vice versa*. In two RCTs,[11,20] OR was not estimable because no patient crossed over (table 3). In the three remaining RCTs[9,10,22] the 95% CI of each study did not include 1 for the OR. In a reanalysis for noncompliance and crossover outcomes, adding a nominal value of 0.5 in all 2×2 cells to enable calculation of ORs and retesting for heterogeneity, no significant difference was found when comparing with the initial analysis.

Discussion

The main pooled results of the present meta-analysis on the effects of NA timing show the following:

- In nulliparous women, on-demand early administration of NA for labor and delivery is not associated with an increased risk of CD and IVD compared with the control group. Laboring women receiving early systemic opioids before late EA have a higher incidence of IVD for NRFS than women receiving early NA.
- Early NA is associated with better neonatal outcomes. When early NA is provided, neonatal UApH values are higher, and less naloxone is used than in the control group. Neonates of women receiving early EA present a higher UVpH than the control group. No difference in neonatal weight was found, and Apgar scores less than 7 at both 1 and 5 min are observed equally often in both early NA and control groups.
- Early NA is a more effective maternal pain relief method, as indicated by lower noncompliance and crossover rates of laboring women. There are no statistically significant differences in prenatal education, first- and second-stage labor duration, or oxytocin use between early NA and control groups.

Cesarean and Instrumental Vaginal Delivery

The question of whether the timing of NA related to cervical dilation affects maternal outcomes is still the subject of controversy. Some studies have reported that early EA is associated with an increased rate of CD and, consequently, the authors of these studies have proposed delaying the initiation of EA until women in labor reach 4–5 cm of cervical dilation.[12–14] However, in these studies, EA timing was analyzed by a retrospective analysis with adjustment for confounding factors based on a propensity score,[12] by a retrospective subgroup approach,[13] or by a *post hoc* analysis.[14] Therefore, the reported "harmful" side effects of early NA initiation on mode of delivery may derive from design and conduct of studies (*e.g.*, inability to prevent systematic errors and analytic bias). All of these studies were excluded from the current meta-analysis because they did not meet quality criteria.[18]

The pooled results of the current meta-analysis show that nulliparous women receiving early NA (≤ 4 cm of cervical dilation) are not at increased risk of CD and IVD. Similar results have been obtained in a perspective CS comparing women (50% nulliparous) receiving early *ver-*

Table 2. Intervention Details of Analyzed Studies

		Early Group Analgesic Interventions		Control Group Analgesic Interventions	
Authors, Year	Labor Protocol–Preload	NA Timing Relative to Cervical Dilation	EA or CSE	NA Timing Relative to Cervical Dilation	Parenteral Opioid and/or Late EA
Chestnut *et al.*,[9] 1994	Oxytocin augmentation (1 mU every 30 min) until an adequate labor pattern; unknown criteria for operative delivery—500 ml RL	Median 3.5 cm	Epidural bupivacaine: 5 ml 0.25% plus additional boluses for T10 level analgesia; 12 ml/h cont. inf. 0.125% with adjusted rate to maintain analgesia and minimize motor block	Median 5 cm	IV nalbuphine: 10 mg repeated if requested 1 h after and if cervical dilation was < 5 cm; at third request or if cervical dilation ≥ 5 cm, EA was given; protocol for EA similar to early group
Chestnut *et al.*,[10] 1994	Oxytocin used (dose not reported); unknown criteria for operative delivery—500 ml RL	Median 3.5 cm	Epidural bupivacaine: 5 ml 0.25% plus additional boluses for T10 level analgesia; 12 ml/h cont. inf. 0.125% with adjusted rate to maintain analgesia and minimize motor block	Median 5 cm	IV nalbuphine: 10 mg repeated if requested 1 h after and if cervical dilation was < 5 cm; at third request or if cervical dilation ≥ 5 cm, EA was given; protocol for EA similar to early group
Luxman *et al.*,[11] 1998	Amniotomy at admission if women without spontaneous ROM; defined criteria for oxytocin augmentation (2 mU every 30 min); unknown criteria for operative delivery—preload not stated	Average 2.3 cm	Epidural bupivacaine: 8 ml 0.25% boluses until full cervical dilation	Average 4.5 cm	No analgesia before 4 cm cervical dilation; protocol for EA similar to early group
Ohel and Harats,[36] 2006	Not stated	≤ 3 cm	Epidural bupivacaine: 0.5% boluses to maintain continuous analgesia; parenteral pethidine used in some patients, but not standardized	> 3 cm	Protocol for EA similar to early group; parenteral pethidine used in some patient, but not standardized
Ohel *et al.*,[20] 1994	Oxytocin used but dose not reported; criteria for operative delivery left to the responsibility of the obstetric team; instrumental delivery performed when failure to progress after full dilation for 3 h (during EA) or 2 h (without EA)—500 ml RL	Average 2.4 cm	Epidural ropivacaine: 10 ml 0.2% plus 50 μg fentanyl; 10 ml/h ropivacaine 0.1% with 2 μg/ml fentanyl cont. inf. to maintain analgesia; IV pethidine and promethazine boluses used in some patients, but not standardized	Average 4.6 cm	IV pethidine and promethazine boluses used but not standardized; protocol for EA similar to early group
Rogers *et al.*,[21] 1999	Active (6 mU oxytocin every 15 min) or traditional (1 mU oxytocin every 30 min) management of labor; diagnosis of dystocia as failure to progress in labor; defined criteria for non reassuring FHR tracing—preload not stated	≤ 4 cm	Epidural bupivacaine: 0.125% plus 50 μg fentanyl or 10 μg sufentanil for T8–T10 level analgesia; 0.08% plus 1 μg/ml fentanyl cont. inf. with adjusted rate to maintain analgesia	> 4 cm	No early analgesia described; protocol for EA similar to early group
Sharma *et al.*,[37] 2003	Written protocol established by medical staff; 6 mU oxytocin every 40 min; diagnosis of dystocia as adequate uterine activity without progressive cervical dilation or descent of the fetal head; unknown criteria for non reassuring FHR tracing—500 ml RL	< 3 cm	10 μg intrathecal sufentanil or epidural bupivacaine: 0.25% for T10 level analgesia; 8–10 ml/h 0.125% plus 2 μg/ml fentanyl cont. inf. with adjusted rate to maintain T8 level analgesia or 6 ml/h 0.0625% plus 2 μg/ml fentanyl cont. inf. and 5 ml of the same solution as PC bolus every 15 min as needed	na	IV meperidine: 50–75 mg boluses every 2 h as needed or initial bolus of 50 mg plus 25 mg promethazine, plus 10–15 mg as PC bolus every 10 min as needed, till a maximum of 400 mg in 6 h
Vahratian *et al.*,[23] 2004	No active management; defined criteria for dystocia; nonreassuring FHR tracing established by medical staff—500 to 1,000 ml RL	Median 4 cm	Epidural bupivacaine: 8 ml 0.125% plus 100 μg fentanyl for T10 level analgesia; 10 ml/h cont. inf. 0.125% plus 2–4 μg/ml fentanyl with adjusted rate to maintain analgesia and minimize motor block	na	IV butorphanol: 2 mg plus 25 mg promethazine
Wong *et al.*,[22] 2005	Defined criteria for nonreassuring FHR tracing; criteria for oxytocin augmentation and for operative delivery established by obstetric management team—500 to 1,000 ml RL	Median 2.0 cm	25 μg intrathecal fentanyl; then epidural bupivacaine: 15 ml/h cont. inf. 0.0625% plus 2 μg/ml fentanyl and 5 ml of the same solution as PC bolus with 10 min of lockout, till a maximal volume of 30 ml/h; rescue treatment with bolus of 10–15 ml 0.125% bupivacaine or 1% lidocaine, with increases in infusion rate or bupivacaine concentration or both	Median 4.0 cm	Parenteral hydromorphone: 1 mg IM plus 1 mg IV repeated if requested and if cervical dilation was < 4 cm; at third request or if cervical dilation was ≥ 4 cm, EA was given; protocol for EA similar to early group except for initial intrathecal fentanyl

Cont. inf. = continuous infusion; CSE = combined spinal–epidural analgesia; EA = epidural analgesia; FHR = fetal heart rate; IM = intramuscular; IV = intravenous; NA = neuraxial analgesia; na = not applicable (early parenteral opioid control group); PC = patient-controlled; RL = lactated Ringer's solution; ROM = rupture of membranes.

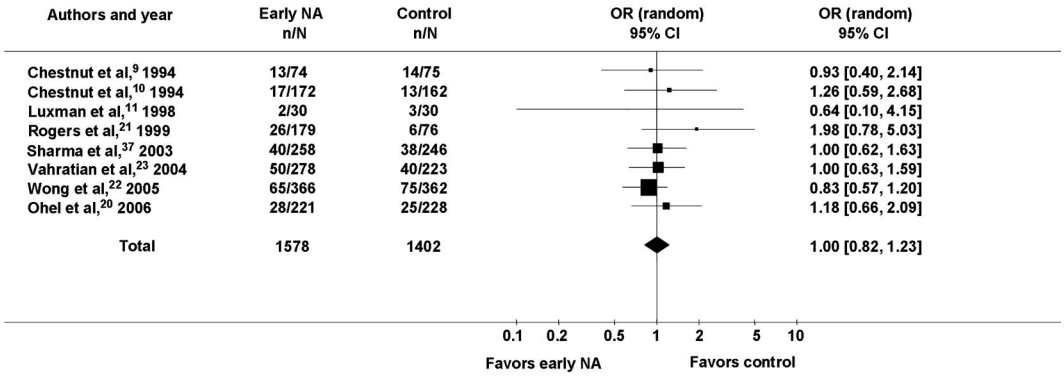

Fig. 2. Rates of cesarean delivery for each of the studies with odds ratios (ORs) and 95% confidence intervals (CIs). The pooled OR and 95% CI are shown as the total. The size of the *box* at the point estimate of the OR is proportional to the number of patients in the study and gives a visual representation of the "weighting" of the study. The *diamond* represents the point estimate of the pooled OR, and the length of the *diamond* is proportional to the CI. n = number of events in treatment or control group; N = total number of patients in treatment or control group; NA = neuraxial analgesia.

sus late EA with timing related to fetal station.[30] A recent meta-analysis by Liu and Sia[3] compared nulliparous women receiving EA *versus* parenteral opioid analgesia, focusing on the effects of low concentration epidural infusions on maternal outcome. No difference in CD rate was observed. However, EA was associated with an increased risk of IVD, even though an investigator bias could not be excluded. As a matter of fact, when studies with elective indications for IVD were excluded from the analysis, Liu and Sia did not find any difference in IVD rate.[3] In the current meta-analysis, it is noteworthy that all of the excluded and included studies—except two Israeli studies[11,36] in which traditional concentration epidural infusions were suspended or replaced by parenteral opioid during labor second stage to minimize potential side effects[4] (table 2)—adopt epidural infusions with a low drug concentration. Apart from this common feature, the results by Liu and Sia[3] are not strictly relevant to our main focus because they do not address the question of the effects of NA timing. However, it is remarkable that different investigations, following separate routes in the field of NA for labor, reach analogous conclusions.

Despite the methodologic heterogeneity among the studies included in the meta-analysis due to the different interventions within the early NA (EA, combined spinal–epidural analgesia, variability in dose of local anesthetic administered alone or with neuraxial opioids) and control groups (early parenteral opioids, late EA, or both) (table 2), we observed a strong statistical homogeneity and consistency for the main outcomes CD and IVD. Similar results were found in the RCT and quality CS subgroup analyses, suggesting that when topics, designs, and analyses are well defined, randomized and observational studies may produce equivalent conclusions.[40,41] Therefore, the obstetric practice of delaying NA is not expected to reduce CD and IVD rates.

By sensitivity analysis, we found that laboring women receiving early parenteral opioid with late EA are at higher risk of IVD for NRFS than those receiving early NA. This finding might be related to the effects of parenteral opioids. Their efficacy on maternal analgesia is largely dose dependent rather than drug dependent,[42] and opioids may indirectly affect the fetus by altering maternal ventilation or uteroplacental flow. Moreover, because an amount of drug readily crosses the placenta,

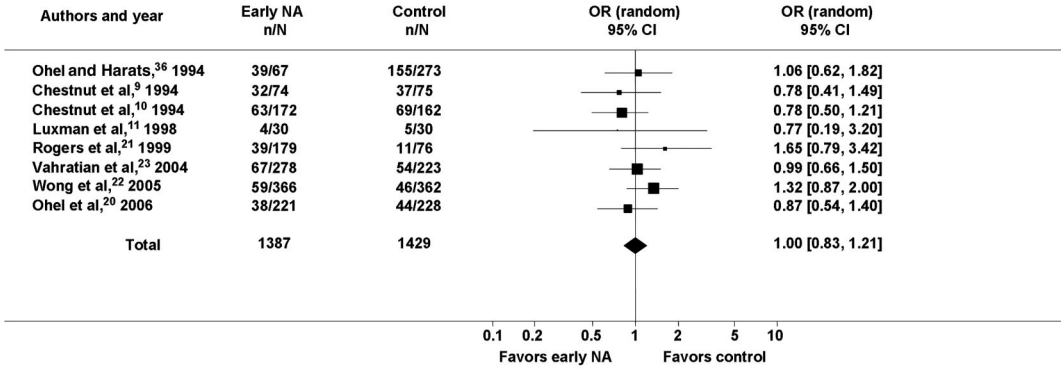

Fig. 3. Rates of instrumental vaginal delivery for each of the studies with odds ratios (ORs) and 95% confidence intervals (CIs). The pooled OR and 95% CI are shown as the total. The size of the *box* at the point estimate of the OR is proportional to the number of patients in the study and gives a visual representation of the "weighting" of the study. The *diamond* represents the point estimate of the pooled OR, and the length of the *diamond* is proportional to the CI. n = number of events in treatment or control group; N = total number of patients in treatment or control group; NA = neuraxial analgesia.

Table 3. Maternal and Neonatal Outcomes

Outcome Measures	No. of Studies	No. of Participants	Studies Included	Early NA, n/N or N	Control, n/N or N	OR or WMD (95% CI)	*P* Value
Cesarean delivery							
Overall	8	2,980	9–11,20–23,37	241/1,578	214/1,402	1.00 (0.82–1.23)	0.97
RCTs	5	1,720	9–11,20,22	125/863	130/857	0.95 (0.72–1.24)	0.70
Quality CSs	3	1,260	21,23,37	116/715	84/545	1.08 (0.79–1.48)	0.61
For dystocia	4	1,660	9,10,20,22	95/833	98/827	0.97 (0.70–1.32)	0.82
For NRFS	3	1,211	9,10,22	22/612	26/599	0.82 (0.46–1.48)	0.51
Instrumental vaginal delivery							
Overall	8	2,816	9–11,20–23,36	341/1,387	421/1,429	1.00 (0.83–1.21)	0.98
RCTs	5	1,720	9–11,20,22	196/863	201/857	0.95 (0.75–1.20)	0.64
Quality CSs	3	1,096	21,23,36	145/524	220/572	1.1 (0.82–1.49)	0.52
For dystocia	2	483	9,10	19/246	18/237	1.02 (0.52–1.99)	0.96
For NRFS	2	483	9,10	30/246	50/237	0.52 (0.32–0.85)	**0.009**
For elective indication	2	483	9,10	46/246	38/237	1.22 (0.76–1.97)	0.41
Neonatal outcomes							
Neonatal weight (g)	6	2,191	9–11,20–22	1,111	1,080	−6.7 (−40.7 to 27.2)	0.70
Apgar score < 7 at 1 min	3	1,211	9,10,22	120/612	138/599	0.89 (0.57–1.40)†	0.62
Apgar score < 7 at 1 min excluding reference 22	2	483	9,10	59/246	51/237	1.15 (0.75–1.76)	0.53
Apgar score < 7 at 5 min	4	1,466	9,10,21,22	12/791	15/675	0.73 (0.33–1.59)	0.42
UApH	3	1,138	9,10,22	572	566	0.02 (0.01–0.02)	**<0.001**
UVpH	3	1,138	9,10,22	572	566	0.01 (0.00–0.03)†	0.11
UVpH excluding reference 22	2	483	9,10	246	237	0.02 (0.01–0.03)	**<0.001**
Naloxone administration to neonates	3	1,194	9,10,22	2/598	18/596	0.16 (0.05–0.55)	**0.003**
Other maternal outcomes							
Prenatal education	2	483	9,10	115/246	124/237	0.82 (0.54–1.23)	0.33
I stage labor duration ratio	6	1,739	9–11,20–22	927	812	0.95 (0.81–1.10)*‡	0.33
II stage labor duration (min)	6	1,690	9–11,20–22	893	797	0.52 (−5.03 to 6.06)	0.86
Oxytocin use	6	2,027	9–11,21–23	797/1,099	710/928	0.83 (0.66–1.05)	0.12
Oxytocin use after randomization/ analgesia	3	1,511	10,20,22	225/759	235/752	0.93 (0.74–1.16)	0.51
Methodologic details							
Noncompliance	5	1,731	9–11,20,22	23/866	120/865	0.14 (0.05–0.39)‡§	**<0.001**
Noncompliance excluding references 9–11	2	1,177	20,22	20/587	62/590	0.30 (0.18–0.50)	**<0.001**
Noncompliance in references 9,10	2	494	9,10	3/249	58/245	0.04 (0.01–0.13)	**<0.001**
Crossover to the other treatment before protocol cervical dilation	5	1,731	9–11,20,22	0/866	61/865	0.02 (0.00–0.11)‖	**<0.001**

* Duration ratio (99% confidence interval [CI]). † Heterogeneity for one trial. ‡ Heterogeneity for two trials. § Not estimable for one trial.[11] ‖ Not estimable for two trials.[11,20]

CS = cohort study; n = number of events in treatment or control group; N = total number of patients in treatment or control group; NA = neuraxial analgesia; NRFS = nonreassuring fetal status; OR = odds ratio; RCT = randomized controlled trial; UApH = umbilical arterial pH; UVpH = umbilical venous pH; WMD = weighted mean difference.

depending on the dose and the route of administration, opioids may directly affect the fetus by decreasing baseline FHR and FHR variability.[43] Hill *et al.*[44] found a greater incidence of abnormal FHR tracing patterns, usually associated with NRFS, in nulliparous women receiving parenteral opioids than in women receiving EA. Therefore, the strategy of delaying EA and providing early analgesia with parenteral opioids may result in a higher risk of IVD for NRFS and may not be advantageous. The two studies included in this sensitivity analysis are from the same institution, and the finding should be confirmed by other groups of investigators, because this result is dependent on adhering to predefined indications for IVD.

Finally, the inferences of our results in clinical practice are that patient factors (women with complicated labor more likely request early NA) and obstetric decisions (labor protocol criteria for dystocia and NRFS not well defined), and not the NA technique itself, are the most likely causative factors of operative delivery.

Neonatal Outcomes

The neonates of laboring mothers receiving early NA are more alert, have less need for naloxone, and have a higher UApH value. Fetal and neonatal status is usually assessed by UApH, umbilical artery base excess/deficit, and arterial partial pressure of carbon dioxide. In a meta-analysis comparing epidural with systemic opioid analgesia, Reynolds *et al.*[45] found that EA is associated with improved neonatal acid–base status, as demonstrated by higher UApH (8 RCTs, 2,322 participants) and umbilical artery base excess (4 RCTs, 1,927 participants).

Analyzing the UVpH, we observed a significant heterogeneity in one trial. Excluding this study, in which early analgesia was provided by using neuraxial opioid (combined spinal–epidural analgesia),[22] heterogeneity vanished and a higher UVpH was found in the early NA group. Because UVpH reflects maternal acid–base status and placental function, this finding could be a result of improved uteroplacental blood flow in the early NA group,[46,47] or of maternal hypoventilation in the group using parenteral opioids.[42]

In summary, these results suggest that fetal–neonatal status is improved with early NA compared with parenteral opioid analgesia.

Neuraxial Analgesia Effectiveness and Maternal Satisfaction

Noncompliance with the assigned protocol and crossover to other treatments are surrogate outcomes for maternal satisfaction and analgesia effectiveness. The lower noncompliance and crossover rates of early NA laboring women suggest that early NA provides superior maternal pain relief than early parenteral opioids and/or late EA. However, significant key differences in participants and interventions among RCTs require a more detailed analysis. The American RCTs with women (Caucasian rates 87%,[9] 80%,[10] and 76%[22]) receiving early parenteral opioid plus late EA presented significant crossover rates (ranging from 3%[22] to 35%[9]). Moreover, a higher number of women in the control group described poor-quality analgesia[9,10,22] and dissatisfaction,[9,10] as evaluated by verbal rating scores. On the contrary, the Israeli RCTs showed that women undergoing late EA considered their childbirth experience satisfactory[20] and did not cross over to receive early EA.[11,20]

Labor pain is a complex phenomenon with sensory, emotional, and perceptive components. The pain threshold may be modified by multiple factors, such as heterogeneity inherent in labor, anxiety, previous suffering experience, and social and cultural influences.[48] Moreover, labor pain is associated with autonomic, psychological, emotional, and behavioral responses.[48] A neuroendocrine response elicited by prolonged and severe pain during labor and delivery causes a decrease in placental perfusion and uncoordinate uterine activity, and may be a cofactor for dysfunctional labor in women at risk.[49] Laboring women requesting NA are at risk for complicated labor because they are often nulliparous, at term, with cephalic presentation in occiput–posterior position, have heavier neonates, are admitted to the hospital with less cervical dilation and higher fetal head station, have slower rate of labor progression, and need oxytocin augmentation.[50] Laboring women requiring more local anesthetic[51,52] or opioid[53] for analgesia more frequently are affected by dystocia. Yet, opioids are inadequate to control the progression of labor pain.[54,55] Whatever the main determining factors of labor pain intensity and their relation with dysfunctional labor (associative or causative), a more effective and safer analgesia, as produced by early NA, should be beneficial and should not be delayed while waiting for further cervical dilation.

Validity Limitations and Research Agenda

The studies included in this meta-analysis, although fulfilling quality criteria,[18] have some limitations due to the peculiarity of the topic. For example, one of the main biases is the lack of blinding of the RCTs,[19] due mainly to the marked differences in the quality of analgesia, because both patients and caregivers can readily differentiate the two analgesic techniques. The lack of appropriate blindness is the reason why no RCT of the current meta-analysis had a Jadad score higher than 3.

Furthermore, only in two RCTs,[20,22] the analysis was performed on an intention-to-treat basis that is more appropriate, although not the perfect solution, when crossover occurs.[27] Labor treatment protocols are crucial to minimize performance bias. The lack of description of FHR interpretation criteria in two trials[9,10] may have introduced an investigator bias. To reduce selection bias, all CSs were selected for predefined homogeneous labor characteristics of comparison cohorts (early NA and control), but the presence of other potential confounders cannot be excluded. Some neonatal outcomes derive only from three RCTs[9,10,22] of two American research groups that published their findings in 1994 and 2005. When their data were pooled, a statistical heterogeneity for effect size, but not for direction, was found. This may have reduced the statistical power of the analysis.

First-stage labor duration ratio has been suggested as an indicator when time 0 is not standardized.[27] However, analysis by using duration ratio is not a validated statistical method in meta-analytic technique; moreover, the use of means instead of medians for describing labor duration may be inappropriate,[27] and therefore, computing a ratio of means, in this context, may not be valid. These limitations, and the statistical heterogeneity of the pooled analyzed studies, suggest that no definite conclusion can be drawn about first-stage labor duration.

The quality of research design has improved in recent times. However, we suggest that future trials on labor analgesia incorporate a patient-oriented approach[56] by adopting accurate, precise, and repeatable criteria to better define those maternal and fetal/neonatal conditions that activate therapeutic interventions, *i.e.*, dystocia and NRFS as indications for operative deliveries.

Conclusions

The current meta-analysis supports no association between patient-requested early NA and overall rate of IVD

and CD and strongly corroborates the current practice guidelines of American Society of Anesthesiologists[7] and recent ACOG Committee Opinion.[16] Early parenteral opioids with late EA are associated with a higher risk of IVD for NRFS, a lower quality of maternal analgesia, and worse indices of neonatal wellness compared with early NA. Therefore, we recommend providing parenteral opioids only when on-demand NA is medically contraindicated.

The obstetric practice of delaying NA is not a sound healthcare policy. Under this perspective, the Obstetric Anesthetists' Association and the Association of Anesthetists of Great Britain and Ireland†† jointly recommended that for giving quality care, where a 24-h epidural service is offered, the time elapsing between the call to the anesthetist and his or her contact with the parturient should not exceed 30 min. Organizational factors such as availability, accessibility, and continuity of obstetric analgesia services, as well as individual and social acceptability, are components of healthcare quality.[4] Nowadays, effective labor pain management is frequently a patient expectation.

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