International Journal of Women's Health

Dovepress
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REVIEW

Progress in analgesia for labor: focus on neuraxial blocks

This article was published in the following Dove Press journal:
International Journal of Women's Health
15 May 2009
Number of times this article has been viewed

J Sudharma Ranasinghe
David J Birnbach

Miller School of Medicine, University of Miami, Florida, USA

Abstract: Neuraxial analgesia is widely accepted as the most effective and the least depressant method of providing pain relief in labor. Over the last several decades neuraxial labor analgesia techniques and medications have progressed to the point now where they provide high quality pain relief with minimal side effects to both the mother and the fetus while maximizing the maternal autonomy possible for the parturient receiving neuraxial analgesia. The introduction of the combined spinal epidural technique for labor has allowed for the rapid onset of analgesia with minimal motor blockade, therefore allowing the comfortable parturient to ambulate. Patient-controlled epidural analgesia techniques have evolved to allow for more flexible analgesia that is tailored to the individual needs of the parturient and effective throughout the different phases of labor. Computer integrated systems have been studied to provide seamless analgesia from induction of neuraxial block to delivery. New adjuvant drugs that improve the effectiveness of neuraxial labor analgesia while decreasing the side effects that may occur due to high dose of a single drug are likely to be added to future labor analgesia practice. Bupivacaine still remains a popular choice of local anesthetic for labor analgesia. New local anesthetics with less cardiotoxicity have been introduced, but their cost effectiveness in the current labor analgesia practice has been questioned.

Keywords: labor, neuraxial, analgesia, neuraxial labor analgesia

Introduction

Labor is one of the most painful situations a human can experience. It was rated more painful than cancer pain and as painful as amputation of a digit without anesthesia.[1]

Labor pain when unrelieved can have adverse effects on the course of labor as well as on the fetal wellbeing.[2] Although various techniques such as inhaled nitrous oxide, parenteral opioids, and alternative therapies (including acupuncture, hydrotherapy, or trancutaneous electrical nerve stimulation) have been employed to lessen the pain and trauma of a painful labor, it is widely accepted that the neuraxial analgesia is the most effective and least depressant form of intrapartum analgesia currently available. Women in pain don't need an "indication" for pain relief in labor. According to the American Society of Anesthesiology (ASA) "in the absence of a medical contraindication, maternal request is a sufficient medical indication for pain relief during labor" (Statement on pain relief during labor, Oct 17, 2007). In addition, they state that neuraxial analgesia should not be withheld on the basis of achieving an arbitrary cervical dilatation.

Epidural analgesia has been used to alleviate labor pain for almost 50 years.

Historically, labor analgesia was administered as a single shot injection of large volume of local anesthetic through the epidural needle. This required repeated epidural

Correspondence: David J Birnbach
Department of Anesthesia, University of Miami Miller School of Medicine, Miami, 1611 NW 12th Avenue, FL 33136, USA
Email dbirnbach@miami.edu

procedures since analgesia was short lived. Not only this method was unsatisfactory there were several maternal deaths due to unrecognized intravascular and intrathecal administrations.[3] Subsequently, heightened awareness and widespread adoption of safer anesthetic practice resulted in several changes in the technique for administration of labor epidural analgesia. These include use of epinephrine containing test dose and fractionation of epidural injections. With the advent of epidural catheters, repeated administration of supplemental analgesia was facilitated without the need for repeated epidural needle insertion or direct injection of medications through the needle. Because of its minimal motor block compared to sensory block, bupivacaine became the popular choice for labor analgesia. However, the high concentration of local anesthetic that was used before late 1980s led to high incidence of motor blockade and other unwanted effects such as maternal hypotension.

Addition of neuraxial opioids permitted reduction in the concentration of bupivacaine from 0.5% to as low as 0.065% while maintaining effective analgesia, and minimizing potential adverse effects on the progress of labor and lower extremity motor block. Combined spinal epidural and/or epidural with low dose local anesthesia may allow women to ambulate while in labor (termed in the lay press "the walking epidural"). New levo isomer local anesthetics, ropivacaine and levobupivacaine have been introduced in recent years, which may be less cardiotoxic than bupivacaine.

There is no question that neuraxial labor analgesia is the most effective pain relief method in labor. However, there are situations where neuraxial methods are not possible because of contraindications (such as maternal coagulopathy, hypovolemia, generalized sepsis) or due to patient refusal. Opioids are the most commonly used parenteral medication for labor analgesia. Unfortunately, for many parturients opioids only provide mild to moderate analgesia in safe doses that is those that do not result in maternal sedation, respiratory depression or neonatal depression. Remifentanil is a potent, ultra-short acting opioid with a rapid onset and offset of action regardless of the duration of administration. It is unique in that it is hydrolyzed by non-specific blood and tissue esterases and has no active metabolites.[4] Remifentanil is shown to produce effective labor analgesia with minimal maternal or neonatal sequale.[5] Although it crosses the placenta, it appears to be rapidly metabolized and/or redistributed in the fetal circulation. Currently, we are developing a system that senses uterine contractions and times the delivery of remifentanil to occur approximately one minute prior to the contraction, so that the maximum analgesia effect falls within the peak contraction period.

This review focuses on current methods and the recent progress of neuraxial labor analgesia techniques.

Initiation of labor analgesia

Combined spinal-epidural (CSE)

The CSE technique is gaining popularity in obstetric practice to provide optimal analgesia for parturients because it offers the possibility of combining the rapid onset of subarachnoid analgesia with the flexibility of continuous epidural analgesia. The duration of spinal analgesia is between 2 and 3 hours, depending on which agent or agents are chosen. The duration of spinal analgesia, however, was shown to decrease when administered to a woman in advanced labor.[6] The original description of spinal analgesia involved sufentanil or fentanyl, but the addition of isobaric bupivacaine to the opioid produces greater density of sensory blockade with longer duration while still minimizing motor blockade.[7] Originally, 25 μg of fentanyl or 10 μg of sufentanil with 2.5 mg of bupivacaine was advocated, but more recent studies have suggested using smaller doses of opioid combined with smaller doses of local anesthetic.[8] The ED_{50} of intrathecal fentanyl for this purpose has been shown to be 14 ± 1 μg and for sufentanil 4.1 ± 0.3 μg.[10] Many clinicians now routinely use 5 μg of sufentanil or 15 μg of fentanyl intrathecally. Fentanyl is widely used as an intrathecal agent for labor analgesia because of its low cost, rapid onset and profound analgesia without motor blockade. Intrathecal fentanyl provides a long enough duration of analgesia for an epidural infusion started immediately after intrathecal injection to reach therapeutic analgesic levels, thus creating a 'seamless' transition from spinal to epidural. Serious maternal side effects of intrathecal fentanyl are infrequent.

Recent studies have suggested that ropivacaine and levobupiacaine can be substituted for intrathecal bupivacaine to provide labor analgesia.[11,12] Teoh et al reported that patients who received hyperbaric bupivacaine had a longer median duration of analgesia (122 min; range 80–210 min) than those who received plain bupivacaine (95 min; range 75–125 min) ($p < 0.01$). The hyperbaric group also had a more limited dermatomal spread (T8 versus T4) while side effect profile was similar in both groups.[13]

Advantages of CSE for labor

Confirmation of epidural needle placement

The appearance of CSF in the hub of the spinal needle during the spinal portion of the CSE confirms the correct placement

of epidural needle. This is especially important in obese patients with increased skin to epidural space distance or those with difficult anatomic landmarks.

Higher success rate with the block

When compared with conventional epidural analgesia for labor, the incidence of overall failure, accidental intravascular placement of epidural catheter, inadequate epidural analgesia, and catheter replacements were shown to be significantly lower in patients receiving CSE analgesia.[14] This difference may be due to the option to confirm questionable epidural needle location by successful spinal injection.[15]

Ambulatory labor analgesia

When CSE is performed with subarachnoid opioids (with or without small analgesic doses of local anesthetics) there is minimal motor blockade, therefore allowing the parturient to ambulate. The desire for mobility during labor further increased the interest in CSE technique. Although it was formerly thought that maternal ambulation could speed the progress of labor, to date the evidence has not been conclusive.[16,17] According to the 2001 obstetric anesthesia work force survey, almost all hospitals allowed ambulation during spinal opioids administration, but much smaller percentage of patients actually ambulated.[18]

In clinical practice the degree of motor blockade is often assessed using the Bromage/modified Bromage scale.[19] To enable ambulation in labor, all muscle groups innervated by the L5-S1 nerve roots should have normal or "near normal" power (Bromage score 0).

CSE: more rapid cervical dilation?

Tsen et al reported that CSE analgesia, when administered to nulliparous parturients in early labor, resulted in significantly more rapid cervical dilatation compared with standard epidural analgesia.[20] This finding was validated by Wong et al who similarly found that spinal opioids were associated with a faster dilatation.[21] The mechanism of rapid cervical dilatation with CSE is unknown. It may be related to reduction in local anesthetic exposure when compared with epidural analgesia, or more likely due to rapid reduction in maternal catecholamines secondary to immediate pain relief with CSE analgesia. In vivo, it has been suggested that epidural bupivacaine may directly slow uterine activity.[22] Clinical studies also support the proposition that maternal epinephrine may be a tocolytic and its reduction may enhance uterine contractions.[2] This mechanism may be related to reports of uterine hypertonia and fetal bradycardia that infrequently occur following CSE labor analgesia

Despite these advantages, the obstetric anesthesia workforce survey reported that less than 10% of all hospitals use CSE in the year 2001.[18] Although CSE seems to be a straightforward technique, there still remain some concerns.

Table 1 Modified bromage score

Score	Description
0	No paralysis, raises extended leg, full flexion of knee and ankle
1	Inability to raise extended leg, able to move knee
2	Inability to flex knee, able to flex ankle
3	Inability to move lower limb

Concerns of CSE for labor

All neuraxial techniques may be associated with complaints of back pain and neurologic complications, but most neurologic complications are associated with pregnancy and delivery, not the anesthetic.[23,24]

Dural puncture and post dural puncture headache (PDPH)

The incidence of PDPH after CSE technique is controversial. It might be argued that the intentional dural puncture involved in the CSE technique would increase the risk of PDPH in obstetric patients compared with those receiving epidural analgesia alone. However, the use of small-gauge atraumatic pencil point spinal needles, such as Whitacre, Pencan, Sprotte, and Gertie Marx, greatly reduce the incidence of PDPH in patients receiving CSE.[25] Norris and coworkers[26] reported that the patients who received only epidural analgesia were more likely to suffer accidental dural puncture (two-fold increase; epidural vs CSE = 4.2%:1.7%). These investigators offered two possible explanations for this result. First, they most often choose CSE for women who are in early labor and reserve epidural analgesia for patients in the more painful active phase of labor. Therefore, the patients in the epidural group may have been more likely to move during the procedure, and thus cause a 'wet tap'. Second, during CSE if one is uncertain of the location of the epidural needle, the spinal needle can be inserted to look for CSF or closeness to dura.

Administration of intrathecal opioids has been shown to decrease the incidence of PDPH.[27] Subsequent infusion of an epidural local anesthetic infusion also may help to decrease the incidence of PDPH (possible tamponade effect?) following CSE.

Risk of catheter migration

Although CSE block with the needle-through-needle technique has recently become increasingly popular, the risk of epidural catheter migration through the dural hole made by the spinal needle has been a concern to many. Holmstrom et al[28] performed a percutaneous rigid epiduroscopy study to assess the risk of catheter migration during CSE and found that it was impossible to force an 18-G epidural catheter through the dural hole after a single dural puncture made by a 25 G spinal needle. After multiple (five) dural punctures with the spinal needle, the epidural catheter penetrated the perforated dura in 1 in 20 cases. For those clinicians who remain concerned about intrathecal catheter migration, special epidural needles with back holes to reduce this risk are currently available from several manufacturers.

Increased drug leakage through the dural puncture

Leighton and collegues[29] reported that following CSE, a dose of epidural local anesthetic will produce a higher dermatomal level than expected, presumably due to subarachnoid flux of the drug. This effect however was quite small and when used for labor analgesia, unless the dura is breeched with the epidural needle or a large bolus volume is administered, flux should not be clinically significant.

Infectious complications

Theoretically, CSE could be associated with an increased risk of meningitis compared with epidural alone because the dura (protective barrier for CNS) is punctured deliberately during CSE and then a foreign body (an epidural catheter), is placed nearby. Contamination of the subarachnoid space may occur from bleeding due to needle trauma in a bacteremic patient or from failure of aseptic technique. Phillips and coworkers[30] reported no cases of meningitis after a prospective review of 10,440 cases of spinal anesthesia in patients undergoing obstetric and urological operations, which are known to be associated with perioperative bacteremia. However, case reports of meningitis following CSE appeared in the journals beginning mid 1990s.[30–32] There was also a case of aseptic meningitis associated with the spinal component of the CSE technique.[33]

Headache and neck pain or neck stiffness in a patient who recently had spinal anesthesia is often attributed to PDPH. One case report[34] highlighted the danger associated with missed diagnosis. Her condition deteriorated, and meningitis was not considered as a diagnosis until it was too late and the patient subsequently died in an intensive care unit.

Contamination of CSF with metal particles

It has been alleged that during the needle-through-needle (NTN) CSE technique, tiny metal particles abraded by the spinal needle from the inner edge of the Tuohy needle may be introduced into the epidural or spinal compartment.[35] In order to examine this concern, Holst and collegues[36] simulated the NTN technique in an in-vitro model. They reported no increased alloy components detected in the rinse solution after either twofold or fivefold puncture compared with the control measurements. No traces of abrasion could be detected by electron microscopy on the inner ground edge of the Tuohy needle either.

Fetal bradycardia

The cause of fetal bradycardia after CSE remains unclear, but it may be related to an acute reduction in circulating maternal catecholamine levels after the quick onset of analgesia. In addition, it has been postulated that an imbalance between epinephrine and norepinephrine levels cause unopposed alpha-adrenoceptor effects on uterine tone and decreases uterine blood flow. However, preliminary reports suggest that there may be no alteration in uteroplacental blood flow.[37] The reported incidence of prolonged decelerations ranges from 3.9% to 12%, and some required emergency cesarean delivery. However, it seems the doses of intrathecal opioids used by these practitioners were relatively high by current standards (ranging from 50 μg of fentanyl to 7.5 μg to 10 μg of sufentanil).[38] When lower doses of intrathecal opioids were used, CSE analgesia was shown not to be associated with adverse outcome for the fetus. A retrospective study[39] involving 1240 patients who received neuraxial labor analgesia (mostly CSE), and 1140 patients who received systemic medications or no analgesia, demonstrated no significant difference in the rate of cesarean delivery with rates of 1.3% and 1.4%, respectively. That study also reported no emergency cesarean deliveries for acute "fetal distress" in the absence of obstetric indications up to 90 minutes after intrathecal sufentanil administration.

Untested epidural catheter

The function of the epidural catheter inserted with the CSE technique is uncertain until after the duration spinal analgesia. Although there are concerns about the unknown location of the catheter if an emergency procedure is required within one to two hours of CSE placement,[40] this issue seems to have been addressed. Epidural catheters inserted via needle through needle technique were demonstrated to have a higher probability of being in the epidural space as compared to

catheters inserted in the stand-alone epidural technique.[41] The author of one study suggested 'laboring women at risk for operative intervention can safely receive CSE analgesia'.

CSE technique appears cumbersome and time consuming

Newer CSE trays have helped to eliminate preparation time. It is believed that in experienced hands the entire procedure should not take longer than a few minutes.[42]

Side effects of intrathecal opioids-

Itching, nausea and vomiting, hypotension, and respiratory depression have all been reported following appropriate doses of spinal fentanyl or sufentanil. A recent report of a dramatic overdose of intrathecal opioid for labor (45 mcg sufentanil as part of a CSE) demonstrated intense pruritus as well as difficulty swallowing, but incomplete pain relief for the second stage of labor.[43]

Itching

Itching (facial or generalized) commonly occurs after administration of intrathecal opioids. The reported incidence of this side effect after intrathecal sufentanil is between 33% and 95%.[44] The incidence may approach 100% after intrathecal morphine.[45]The mechanism of itching appears to be complex. One theory suggests that facial itching is mediated by a specific opioid effect in the medullary dorsal horn.[46] Activation of the serotonergic system is also considered as an important factor in the pathogenesis of intrathecal opioid-induced pruritus.[47] Most often this itching is mild and transient and only rarely requires treatment. Studies that ask patients specifically about itching report a higher incidence.[44] The addition of intrathecal local anesthetic has been shown to reduce the risk of opioid-induced itching.[48]

Nausea and vomiting

Like itching, nausea and vomiting may also occur more often with CSE than conventional epidural analgesia.[25] However, the incidence of this side effect is relatively low (2.4%–3.2%).

Hypotension

Hypotension (SBP $<$ 90 mmHg) is well recognized after epidural local anesthetics, and studies have reported a 17% to 28% incidence during epidural labor analgesia.[49] Hypotension has also been reported in up to 14% of parturients receiving either intrathecal fentanyl/morphine[50] or intrathecal sufentanil[44] for labor analgesia. The mechanism of hypotension after intrathecal opioids is unclear. A weak local anesthetic effect[44] or an action on opioid receptors located in the preganglionic sympathetic nerve fibers[51] has been suggested. However, it has been reported that in humans sympathetic nerve activity remains unchanged after intrathecal morphine.[52]

Norris et al reported a similar effect on systolic blood pressure by both labor epidural and CSE.[26] He reported 7.9% incidence of hypotension after intrathecal sufentanil, a much lower incidence than the other studies. Some agree that the hypotension may be simply related to pain relief.

Respiratory depression

Although exceedingly rare in parturients receiving lipid soluble neuraxial opioids, it has been reported that neuraxial opioids may be associated with a clinically significant respiratory depression which may even lead to fatal consequences.[53] Non-obstetric studies report 0.01% to 7% incidence of respiratory depression after neuraxial opioids.[53,54] Lipophilic opioids such as fentanyl and sufentanil, which are commonly administered intrathecally during CSE, may rarely cause early-onset respiratory depression typically within 30 min. This is likely due to the significant vascular uptake[55] via subarachnoid vascular plexuses or rostral spread via cerebrospinal fluid.[56] Due to the risk of respiratory depression, the ASA Task Force recommends that after neuraxial lipophilic opioids continual respiratory monitoring should be performed for a minimum of 2 hour after bolus administration or discontinuation of the infusion.[53,57]

Comparison of CSE with conventional epidural technique for labor analgesia

Many studies have compared CSE with straight epidural analgesia technique. Norris et al[58] performed a prospective, quasi-randomized clinical trial in a large number of women (2183 laboring women) comparing needle-through-needle CSE and epidural labor analgesia. The primary outcome studied was mode of delivery (spontaneous vaginal, operative vaginal, or cesarean). Important secondary outcomes included neonatal condition (as measured by Apgar score and umbilical artery blood gas values) and anesthetic complications and success. They found no difference in obstetric or neonatal outcome that could be explained by the choice of anesthetic technique. There was no increased incidence of positional headache due to intentional dural puncture with the 27 gauge (pencil point) spinal needle in the CSE group. Later, Miro et al also confirmed the safety of CSE, with similar findings, in a retrospective study involving 6497 cases.[59]

Test dose controversy

The issue of whether a test dose is needed prior to initiating an epidural infusion for labor with ultra-dilute local anesthetic has been questioned.[60,61] Currently, many anesthesiologists avoid the "classic" test dose (1.5% lidocaine with epinephrine 1:200,000) and argue that the unintentional IV administration of an ultra-dilute solution of local anesthetic such as less than 0.1% bupivacaine with fentanyl, could not possibly harm a patient. After several hours, the infusion itself becomes a test; if the epidural catheter is intravascular, the patient should have no pain relief; if the catheter is subarachnoid, a solid motor block would develop. If the patient remains comfortable and without a motor block, a proper epidural catheter placement is highly probable. The test dose that contains concentrated local anesthetic and epinephrine can increase the motor block of the subsequent epidural and therefore reduce the possibility of walking.[62]

However, this argument fails to consider the patients who require an emergency cesarean delivery before the recognition of an intravascular catheter. Although infusions of ultra-dilute local anesthetics do not pose a serious threat, such is not true of concentrated local anesthetics used for operative delivery. Therefore, use of a test dose should be considered when administration of large doses of high concentration local anesthetic through the epidural catheter is required such as operative delivery.

Fluid preloading

It is the standard practice in many institutions to administer a fluid preload prior to initiation of neuraxial labor analgesia. Fluid preloading is thought to reduce hemodynamic changes, specifically hypotension, caused by labor epidural. Collins et al in 1978, showed that fluid preloading significantly reduces abnormalities in fetal heart rate (FHR) (34% to 12%) and maternal hypotension (28% to 2%) during epidural analgesia.[63] They excluded patients with preeclampsia and pre-existing hypertension. However, Collins original study used bupivacaine 0.375%, a concentration that is not commonly used in current practice, and probably the cause for significant hypotension. Recent investigators questions the relevance of fluid preloading in current epidural practice because they were not able to show a statistically significant increase in the incidence of maternal hypotension when intravenous preloading was omitted before labor epidural using a low concentration bupivacaine.[64,65] A study by Kinsella et al also showed similar findings using a low concentration bupivacaine during labor epidural.[66] However, new abnormalities in FHR tracing occurred in 11% and 30% of the preload and no preload groups, respectively. Although this did not reach statistical significance, it may be cause for concern. Is fluid loading beneficial to FHR tracing (fetus)? Cheek et al performed a study to observe the effects of intravenous fluid infusion on uterine activity during normal labor in women receiving epidural analgesia. There was a decrease in uterine activity after a one-liter fluid bolus, which returned to baseline over the next 20 minutes. There was no hypotension in the group that did not receive fluid preload. Epidural block has no effect on the uterine activity.[67] The authors speculated that the mechanism of decreased uterine activity lie either in a release of atrial natriuretic peptide (ANP) after atrial distension with fluid bolus or due to release of vasoactive peptides by the uterine vascular endothelium. It is possible that reduced uterine activity from a fluid bolus cause the positive effects on the FHR tracing. Rham et al[68] reported a fall in the plasma oxytocin concentration one hour after initiation of labor epidural analgesia. He concluded that epidural analgesia may interfere with the release of plasma oxytocin, and may be one mechanism behind prolongation of labor. The epidural may, however, be one of many factors and is unlikely to be primarily related.

Fluid preloading may be beneficial prior to labor epidurals in situations where fetus is at increased risk. However, routine use of preload in current epidural practice is questionable and may lead to prolonged labor due to decreased uterine activity.

Maintenance of labor analgesia

Continuous epidural infusion

Currently, the most commonly used technique for maintenance of labor analgesia is continuous epidural infusion, which avoids a number of problems that had been associated with intermittent bolus techniques, such as uneven analgesia and possible increased infection rate. With the advent of automated infusion pumps, continuous infusion of epidural medications via an indwelling catheter became possible. New forms of epidural analgesia use combinations of opioid and lower concentration of local anesthetic which preserve maternal motor function and allow parturients to ambulate. The COMET study, a randomized controlled trial[69] (Comparative Obstetric Mobile Epidural Trial) compared traditional epidural analgesia for labor using high concentration local anesthetics (bupivacaine 0.25%) with two types of low dose techniques, namely CSE and continuous low dose infusion (bupivacaine 0.1% with fentanyl) in 1054 nulliparous women requesting epidural pain relief. The authors reported that the low-dose epidural

analgesia resulted in significantly more vaginal deliveries than traditional technique. They estimated that almost one in four operative vaginal deliveries could be prevented by the introduction of low dose epidural analgesia. Cesarean delivery rates between traditional and low dose techniques did not differ. The quality of analgesia was the same with all methods, indicating that the benefit achieved by the low-dose techniques do not compromise pain relief. They concluded that "in relation to delivery outcome, continued routing use of traditional epidurals might not be justified".

Automated intermittent bolus

The maintenance of labor analgesia after intrathecal induction with a CSE technique is commonly achieved with the use of a continuous epidural infusion, which is usually initiated prior to regression of spinal analgesia. A study by Sebastian et al showed that employing a regimen of regularly scheduled automated intermittent boluses one could improve the analgesic function of the epidural catheter.[70] Experimentally, it has been shown that the spread of an infusate from a multi-orificed catheter is more extensive if regular boluses were used instead of a continuous infusion, despite a similar rate of discharge. Kaynar and Shankar[71] demonstrated at low injection pressures the flow through a multi-orifice catheter is largest from the proximal hole and no flow occurred from the distal port. During bolus injection, the solution flowed through all the ports and caused wide spread of the solution. This wider spread probably contributes to better quality of the block in the intermittent bolus technique. In the future, infusion devices may become available to allow programmed boluses. Wong et al[72] in a randomized, double-blind study, compared total bupivacaine consumption, need for supplemental epidural analgesia, quality of analgesia, and patient satisfaction in 158 multiparous term women who received programmed intermittent epidural boluses (PIEB) compared with continuous epidural infusion (CEI) for maintenance of labor analgesia. They reported that compared to CEI group in the PIEB, the median total bupivacaine dose per hour of analgesia was less, fewer manual rescue boluses were required, and satisfaction scores were higher. Labor pain, patient-controlled epidural analgesia (PCEA) requests, and delivered PCEA doses did not differ. They concluded "PIEB combined with PCEA provided similar analgesia, but with a smaller bupivacaine dose and better patient satisfaction compared with CEI with PCEA for maintenance of epidural analgesia".

Previous studies also have shown that intermittent manual bolus injection has a dose-sparing effect on total local anesthetic consumption compared with CEI.[73] Chua and Sia[74] also observed that PIEB is a good alternative to CEI for the maintenance of epidural analgesia after CSE. They observed that the PIEB prolonged the duration and quality of analgesia.

Patient-controlled epidural analgesia (PCEA)

First described for use in labor by Gambling et al[75] in 1988, PCEA allows the parturient to self-administer intermittent boluses of epidural medication, thus providing flexibility to accommodate changing analgesic requirements as labor progresses. The anesthesiologist adjusts the PCEA program settings such as demand bolus, lockout interval, background infusion rate and hourly maximum rate for individual patients. PCEA allows better dose-demand matching as labor progresses, and therefore is shown to be associated with reduced total volume of local anesthetic requirements, especially in the first stage of labor.

In the classic study by Gambling[75] the patients were randomized to receive 0.125% bupivacaine as a (CIEA) continuous infusion (12 mL/hour) or under PCEA setting (4ml basal, 4 mL bolus as required up to 16 mL/hour). Patients in the PCEA received significantly less local anesthetic than those in the CIEA group, and appreciated control over their own pain relief with less reliance on medical staff. A significant reduction in hourly dose requirements, varying from 17% to 47%, has been shown by various studies when compared with continuous infusions.[76–81] Anesthesiologist-delivered supplemental "top-ups" and anesthesia personal work load is also shown to be reduced when PCEA mode is used.[82] Although PCEA is claimed to have several advantages, according to the most recent obstetric anesthesia work force survey,[18] only 18% to 35% of hospitals in the US employ PCEA. The reason for this low use in unclear, possibly due to unfamiliarity or equipment cost.

Gambling et al also performed a double-blind, prospective study[79] to determine the optimal initial combination of bolus dose and lockout interval for PCEA. He compared 4 different bolus-only PCEA combinations with a CIEA group (8 mL/hour). Each group received 0.125% bupivacaine with 1:400,000 epinephrine and fentanyl 2.5 μg/mL. This study was designed to answer 2 questions. (1) Does it matter which PCA dose variables are used to set up PCEA in labor? (2) Is PCEA, without a background infusion, as effective as CIEA? He reported, "There were no differences seen among four dosing programs chosen for PCEA in labor. Patients in each group experienced similar degrees of satisfactory pain relief,

and this was comparable to the analgesia provided by constant infusion." The bupivacaine and fentanyl consumption were less in PCEA groups than in the CIEA group.

Continuous epidural infusion (CEI) with PCEA

PCEA can be administered as demand dosing (DD) only mode or as continuous epidural infusion plus DD mode. Demand dosing involves a fixed amount of drug administered by the patient by pressing the PCA button without concomitant use of a continuous background infusion. With continuous infusion plus demand dosing, a continuous background infusion is prescribed and the patient can administer supplemental doses by pressing the PCA button. The role of the background infusion (CEI) in the PCEA setting seems to be still unclear in the literature. While some authors suggest that the CEI with PCEA increases drug consumption without an analgesia benefit,[83,84] other studies have demonstrated reduced need for analgesia supplementation with CEI. Ferrante et al[85] performed a study to determine whether there is any advantage for a background infusion during PCEA for labor and delivery. They randomized 60 nulliparous or parous women in labor at term to one of four groups to receive either continuous epidural infusion (CEI) or three PCEA groups in a double-blind fashion. All patients received 0.125% bupivacaine with 2 μg /mL of fentanyl through the PCA infuser. CEI group received the epidural infusion at 12 mL/hour. The three PCEA groups received either no background epidural infusion, or CEI at a rate of 3 mL/hour or 6 mL/hour. The findings of their study were as follows: The patients receiving fixed-rate CEI had a lower incidence of spontaneous delivery ($p < 0.04$). All modes of PCEA provided equivalent pain scores, extent of sensory, degree of motor blockade, and cumulative hourly bupivacaine use. However DD only PCEA, and provision of a minimal background infusion (CEI 3 mL/hour) were associated with a trend towards increased necessity for physician administered supplemental bupivacaine, which may be difficult to quickly achieve in a busy obstetric unit. The group, CEI 6 mL/hour + DD PCEA received 33% of its maximum hourly demand dose as a background infusion and the need for physician administered supplementation was minimal. Therefore, according to this study, administration of a modest proportion (33%) of the maximum hourly demand dose as a background infusion would appear optimal when PCEA is used for labor analgesia.

Computer-integrated patient-controlled epidural analgesia (CI-PCEA)

In a PCEA mode, the basal infusion (CEI) appears to play an increasingly important role as pain intensifies with the progress of labor or with the initiation of labor augmentation regimens. In order to achieve seamless analgesia (defined as one without breakthrough pain from induction of block to delivery), Sia and colleagues[86] made a further improvement in the CEI-PCEA mode. He devised a program (based on a clinical algorithm) that converts an ordinary continuous infusion pump to a PCEA pump. The pump analyses the patient's needs in the previous hour (based on the PCEA needs) and automatically adjusts the basal infusion accordingly. Therefore, the basal infusion rate would be automatically increased for a patient who makes more demands. They called this computer-integrated PCEA (CI-PCEA). In his pilot study, which compared CEI only to CI-PCEA, he demonstrated that CI- PCEA reduced the incidence of breakthrough pain. However, these authors were not able to demonstrate a difference in the hourly consumption of local anesthetics or patient satisfaction between the two groups. In a follow up study done by Lim et al the breakthrough pain requiring anesthetic supplementation was lower in the CI-PCEA group (15%–35%), but this difference was not statistically significant. However, the CI-PCEA group reported significantly higher maternal satisfaction scores.[87]

New local anesthetics

Bupivacaine has been the standard local anesthetic for epidural labor analgesia for many years. It has many advantages when used for labor analgesia; the quality of analgesia is high in relation to the degree of motor block, the duration is long, and it is generally not associated with tachyphylaxis, as seen with lidocaine.[88] Unfortunately, a number of cases of toxic reactions and refractory cardiac arrests[3] have been associated with bupivacaine, most involving obstetric patients, and 0.75% bupivacaine is now proscribed from obstetric practice. Animal studies[87] have confirmed that bupivacine is more cardiotoxic than lidocaine, a mechanism relating to its action on the cardiac sodium channels. Lidocaine blocks channels in a fast-in-fast-out fashion. Bupivacaine was found to be a "fast-in, slow-out" agent. The reason for increased incidence of fatal systemic toxicity to bupivacaine in pregnancy may be due to many factors.[90] These include: (1) more frequent use of bupivacaine for epidural blocks, especially in high concentrations prior to the late 1970s, (2) it is easier to accidentally puncture dilated epidural veins during pregnancy (3) physiological changes of pregnancy makes

them more susceptible to such reactions (4) resuscitation is more difficult in a parturient.

The appreciation of the cardiotoxicity of bupivacaine in the late 1970s led to two important changes: First, the heightened awareness, widespread adoption of safer anesthetic practice including test doses, fractionation of epidural injection, and use of dilute solutions by continuous infusion. Hawkins et al[91] reported no maternal deaths due to bupivacaine-induced cardiotoxicty in the analysis of maternal mortality during the period of 1979 to 1990. Second, is the development of newer local anesthetics with less intrinsic toxicity.

The two new local anesthetics, levobupivacaine and ropivacaine have been compared to bupivacaine and shown to provide very satisfactory labor analgesia with a possible reduced incidence of motor blockade and decreased cardiotoxicity.

Animal models have confirmed the reduced systemic toxicity of these newer anesthetic agents. Santos and DeArmars[92] performed an animal study to compare the systemic toxicity of three local anesthetics (levobupivacaine, bupivacaine, and ropivacaine) and to determine whether pregnancy affect the systemic toxicity. They found that the doses required to produce convulsions were lower in the pregnant animals than in the non-pregnant for all three drugs. However, there were no significant differences in the doses required to produce more advanced manifestations of systemic toxicity such as circulatory collapse and apnea between pregnant and non-pregnant. The risk of toxicity was greatest with bupivacaine and least with ropivacaine. Human volunteer studies also confirm the reduced systemic toxicity of ropivacaine.[93] Both levobupivacaine and ropivacaine have been shown to have less arrythmogenic potential than bupivacaine, and therefore resuscitation seems to be more effective in cases of systemic toxicity.[94,95]

Bader et al[96] compared the effect on motor function of ropivacaine and bupivacaine at equal concentrations using an isolated rabbit vagus nerve model. Their results showed that the depressant effect of bupivacaine was 16% greater on motor fibers compared to ropivacaine. Writer et al[97] performed a meta-analysis involving 403 laboring women who received either ropivacaine or bupivacaine 0.25% (equal strength) as intermittent bolus or continuous bolus for labor epidural analgesia. Their study showed that spontaneous deliveries occurred more frequently with ropivacaine that with bupivacaine (58% vs 49%; $p < 0.05$), and instrumental deliveries were less frequent with ropivacaine (27% vs 40%; $p < 0.01$). The cesarean delivery rates, however, were similar between groups. The motor block was also shown to be lower in the ropivacaine group. However, their study has been criticized as not uniform in the design, results not homogenous, and therefore difficult to draw conclusions.[98] Dresner et al[99] performed a randomized double blind comparison of 0.1% bupivacaine plus fentanyl 2 μg/mL vs 0.2% ropivacaine (double strength) as continuous infusion for epidural labor analgesia. They found no difference in the motor block or mode of delivery between groups. The pain relief and satisfaction scores from midwives and patients were consistently better in the ropivacaine group, but this did not reach statistical significance. Although there seems to be a difference in the motor block between ropivacaine and bupivacaine at diluted concentrations (ie, 0.1%), this difference seems to disappear at higher concentrations (ie, 0.25% or 0.5%).[100–102]

Most of the above comparisons seem to have assumed that the new local anesthetics (ropivacaine and levobupivacine) are equipotent with bupivacaine. This seems to be true with levobupivacine but not with ropivacaine. Lyons et al[103] compared the minimum local analgesic concentrations (MLAC) of levobupivacaine relative to racemic bupivacaine in a prospective, randomized, double-blind, sequential allocation study. They found the potency ratio to be almost equal (0.98) between levobupivacaine and bupivacaine. However, using up-down sequential allocation, Polley et al[104] found the MLAC of bupivacaine to be 0.067% wt./volume (95% confidence interval [CI], 0.052–0.082), the MLAC of ropivacaine to be 0.111% wt./volume (95% CI 0.100–0.122, and the potency ratio between the two to be 0.6 (95% CI 0.49–0.74). Similarly, Capogna et al also found analgesic potency of ropivacaine to be 40% less than that of bupivacaine.[105] Therefore, it has been argued that the modest motor sparing property (even systemic toxicity?) of ropivacaine noted in some studies may merely reflect the potency difference, and must be re-evaluated.[96] However, a study by Dony et al found ropivacaine to be less toxic than bupivacaine even at an equipotent dose.[106]

The new local anesthetics are considerably more expensive than racemic bupivacaine. The approximate incremental cost of substituting ropivacaine for bupivacaine for labor analgesia was calculated to be approximately US$12 per patient.[107] With the widespread use of ultra-dilute epidural infusions of bupivacaine and CSE technique, it is very unlikely that systemic toxicity will be a problem during labor epidural analgesia. There seems to be no clinical justification to use more expensive local anesthetics such as ropivacaine in the current labor analgesia practice. Both laboratory

and clinical studies have failed to show that ropivacaine or levobupivacaine offers any advantage over bupivacine in terms of placental transfer and/or neonatal outcome.[108–110]

New adjuvant drugs

Adjuvant drugs are used to improve the effectiveness of neuraxial labor analgesia and decrease the side effects that may occur due to a high dose of a single drug. Neuraxial opioids are used routinely for this purpose. Recently, several studies have demonstrated the effectiveness of clonidine (an alpha-2 adrenergic agonist) and neostigmine (cholinesterase inhibitor) for labor analgesia or for post cesarean pain relief.[111,112] Clonidine produces analgesia by binding to the alpha-2 adrenergic receptors in the dorsal horn of the spinal cord to inhibit the release of substance P. Neuraxial clonidine also increases acetylcholine levels in the cerebrospinal fluid. Neostgmine increases spinal acetylcholine by preventing its breakdown. Analgesia is produced when acetylcholine binds to the spinal cord receptors (muscarinic and nicotinic) and stimulates the nitric oxide synthesis.[113]

Intrathecal use of clonidine and neostigmine for labor

A small dose of intrathecal clonidine (15–30 μg) when combined with local anesthetics and opioids is shown to produce high quality, rapid onset prolonged labor analgesia but with sedation and hypotension.[111] Therefore, maternal blood pressure must be carefully monitored and treated with ephedrine quickly. Owen et al showed that the duration of analgesia from intrathecal bupivacaine-fentanyl can be significantly increased by the addition of clonidine 30 micg and neostigmine 10 micg.[112] However, intrathecal neostigmine is associated with severe nausea that is unresponsive to standard medications.[112]

Epidural use of clonidine and neostigmine for labor

Paech et al evaluated clonidine as a component of PCEA. He reported that the addition of clonidine (22–45 μg/hour) to bupivacaine (0.0625%) and fentanyl (2 μg/mL) produced better pain relief and reduced the need for PCEA boluses during the first stage of labor.[114] Maternal hypotension caused no fetal consequences when treated promptly. There was reduced motor block with clonidine due to the local anesthetic dose-sparing effect. Neostigmine, however, appears to relieve somatic pain better than visceral pain and also has a low lipid solubility. Higher doses are required to be effective in labor.[115] Epidural clonidine 75 μg with neostigmine 750 μg was shown to be effective in initiating labor analgesia without motor or sympathetic block.[116]

Further studies are needed to evaluate the efficacy and the side effects of these adjuvant drugs before adding to labor analgesia practice.

Effect of epidural analgesia on labor outcomes

This has been a controversial topic for many years and several prospective, randomized trials have been published recently addressing this issue.[117–119] The most recent article published by Wong et al[21] concluded:

1. Neuraxial analgesia with low concentration epidural infusions (bupivacaine 0.0625% with 2 micg/ml of fenatnyl or 0.125% bupivacaine) does not increase the risk of cesarean delivery or instrumental vaginal delivery.
2. Neuraxial analgesia in early labor (<4 cm dilatation) does not increase the rate of cesarean delivery. Compared to systemic analgesia, it provides better analgesia and shorter duration of labor.

Conclusion

The amount of labor pain experienced by a parturient is influenced by many factors. These include oxytocin augmentation, presence of dysfunctional labor, duration and phase of labor, as well as various psychological and socio-cultural factors. The ideal labor analgesia should provide effective pain relief throughout the different phases of labor while tailored to the specific needs of the individual parturient. Over the past decades, neuraxial analgesia techniques and medications have evolved to allow for more flexible and effective analgesia while reducing the density of motor blockade.

Disclosures

The authors declare no conflicts of interest.

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