

Potential impact of epidural labor analgesia on the outcomes of neonates and children

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Abstract

This review summarizes recent evidences regarding the potential influences of epidural labor analgesia (ELA) on the outcomes of neonates and children. Terms and relevant words including “ELA,” “ELA and neonatal outcomes,” “ELA and children’s development,” and “ELA and children’s neurocognitive development” were used to search articles published in PubMed database up to October 2019. Original articles and reviews regarding potential influences of ELA on neonates and children were identified. Relevant references of the selected articles were also screened. The anesthetics used during ELA can be absorbed, enter the fetus, and produce neonatal depression; however, these effects are less severe than those during systematic opioid analgesia. The impact of anesthetic exposure during ELA on children’s neurodevelopment has not been fully studied, but would be mild if any. ELA increases the risk of intrapartum maternal fever; the latter may be harmful to neonatal outcomes. The use of ELA may increase birth injury by increasing instrumental delivery, although long-term adverse events are rare. On the other hand, ELA may reduce maternal depression and, thus, produce favorable effects on neurocognitive development in childhood; but evidences are still lacking in this aspect. ELA may produce both favorable and unfavorable effects on neonates and children. These effects should be discussed with parturient women before making decisions. The potential harmful effects should be carefully managed. The overall impacts of ELA on neonatal and children’s outcomes need to be studied further.

Keywords: Epidural labor analgesia; Neonates; Children; Outcomes

Introduction

The intense pain during labor can induce a series of adverse effects in women, including physiological stress response, uncoordinated uterine contraction, prolonged labor duration, and even post-traumatic stress disorder or postpartum depression.^[1-4] It is one of the most important reasons leading to Caesarean delivery around the world.^[5-7] Labor pain may also produce harmful effects on neonates and children, either directly or indirectly, such as neonatal hypoxia, metabolic acidosis, disorders of cognitive and emotional development, and even death.^[8-12]

Epidural labor analgesia (ELA) is the most widely used method to relieve labor pain.^[13,14] It effectively blocks the afferent nociceptive stimulus and blunts the severity of maternal stress response.^[15,16] Recent studies suggest that its use is associated with reduced risks of postpartum depression^[17,18] and even long-term depression.^[19] Furthermore, ELA may also affect neonates and children, including neonatal status,^[20-22] breast-feeding,^[23-25] and

long-term neurodevelopment,^[26,27] but results are conflicting in this aspect. The purpose of this review is to summarize the evidences related to the influences of ELA on the outcomes of neonates and children.

ELA, Anesthetic Exposure, and Neonatal Depression

Neuraxial labor analgesia is usually achieved with a combination of a long-acting local anesthetic and a lipid-soluble opioid, in order to lower doses of each agent and thus minimize the undesirable side effects.^[28] However, in spite of the very low doses of anesthetics used during ELA, these medications can be absorbed, cross the placenta and enter the fetus. In an early study of Loftus *et al*,^[29] 36 parturient women received epidural analgesia with either bupivacaine alone, bupivacaine with fentanyl, or bupivacaine with sufentanil. They found that all three drugs can be detected in maternal and umbilical venous plasma at the time of delivery. In a case reported by Moore *et al*,^[30] a 39-week pregnant woman received epidural analgesia with a mixture of 0.06% bupivacaine and 2 µg/mL fentanyl for

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11 h (280 µg fentanyl given). At 24 h after delivery, fentanyl could still be detected in the urine of both mother (2.0 ng/mL) and neonate (2.4 ng/mL).^[30] Therefore, both local anesthetics and opioids administered for ELA can arrive neonates and produce effects.

The adverse effects of ELA on neonates have been reported. A retrospective cohort study investigated 2399 children; of these, 1848 were born to mothers who did not receive epidural analgesia and 551 to mothers who did. The results showed that neonates with ELA had a slight but significant decrease of Apgar scores at both 1 and 5 min after birth; furthermore, they had higher proportions requiring resuscitation and neonatal intensive care unit (NICU) admission, and a lower proportion of early breastfeeding.^[31] These findings suggest that, when compared with no or light pharmacological analgesia, ELA may have adverse effects on newborns, although the impacts are mild.

It is generally believed that neonatal depression following ELA is mainly produced by opioids. In a recent cohort study, 400 women received either epidural analgesia or combined spinal-epidural analgesia (with 3–5 µg intrathecal sufentanil). A combination of 0.1% levobupivacaine and 0.5 µg/mL sufentanil was used for analgesia during stage I; whereas only 0.125% levobupivacaine was used for analgesia during stage II. As expected, levobupivacaine consumption was significantly higher in the epidural group; but neonatal Apgar scores did not differ between groups.^[32] On the other hand, the harmful effects of local anesthetics cannot be totally excluded. For example, in an early study, parturient women randomly received epidural analgesia with either sufentanil, combined sufentanil-bupivacaine, or bupivacaine alone. The authors reported that infants with bupivacaine alone had higher irritability score.^[33]

The negative neonatal effects of ELA are less severe when compared with systematic opioid analgesia. In a meta-analysis of randomized controlled trials, the proportion of neonates with 1-min Apgar score <7 was significantly less in the ELA group than in the intravenous meperidine group.^[34] Other authors also reported better results of neonatal Apgar score, neuro-behavioral change, and acid-base status with neuraxial analgesia than with systematic opioids.^[22] This is especially true in high-risk pregnancies. For example, in an early study of David *et al*,^[35] the first-week death in low birthweight babies was less after epidural block than after other methods of pain relief. In another study of pregnant women with estimated fetal weight <1.5 kg, neonates with ELA had higher 1-min Apgar scores, less neonatal cord blood acidemia, and better glucose and calcium levels when compared with intramuscular tramadol analgesia.^[36]

ELA, Anesthetic Exposure, and Children's Neurodevelopment

The potential harmful effects of anesthetic exposure on the developing brain have drawn much attention.^[26,37-39] Until recently, a large majority of clinical studies were performed retrospectively; most of these revealed positive

results, that is, anesthetic exposure during early life is associated with mild but statistically significant neuro-cognitive abnormalities.^[26,40,41] It is true that some well-designed prospective studies reported negative results. For example, in a sibling-matched cohort study, Sun *et al*^[42] reported that there were no significant differences in the intelligence quotient scores during later childhood between 105 sibling pairs with and without early-life anesthesia exposure. In an international multicenter randomized controlled trial, 722 infants younger than 60 weeks of post-menstrual age randomly received sevoflurane anesthesia or awake-regional anesthesia. The resulting cognitive composite scores at 2 and 5 years of age were equivalent between the two groups.^[43,44] It should be noted that, in these prospective studies, the sample sizes were small and might not be powerful enough to detect the slight differences between groups.

Studies investigating the impact of neuraxial labor analgesia on children's neurodevelopmental outcomes are limited. In a population-based birth cohort, 4684 mothers who gave vaginal delivery were enrolled; of them, 1495 received neuraxial labor analgesia. The results showed that the use of neuraxial analgesia during labor was not independently associated with the presence of learning disabilities in childhood (diagnosed before age 19 years).^[27] Considering that the dosages of anesthetics used during neuraxial analgesia are much lower than during general anesthesia, the effects of anesthetics administered for neuraxial analgesia on the neurocognitive development in children would be mild if any.

ELA, Maternal Fever, and Children's Outcomes

Women receiving ELA are more likely to experience intrapartum fever.^[45,46] Fusi *et al*^[47] reported an average increase of 1°C in vaginal temperature over 7 h of ELA; whereas the temperature remained constant during intramuscular meperidine analgesia. Camann *et al*^[48] found that, at 5 h since analgesia, the tympanic membrane temperature was significantly higher in parturient women with epidural analgesia than in those with intravenous nalbuphine. Results of randomized controlled trials also confirmed a higher incidence of maternal fever (≥38°C) during ELA.^[49-52]

The underlying mechanisms leading to increased maternal fever during ELA remain unclear but may include the following. First, ELA changes the regulation of body temperature; that is, it results in an imbalance between heat-production and heat-dissipation and, subsequently, maternal fever.^[47,48,53-56] Second, maternal inflammatory disease, such as chorioamnionitis and placental inflammation, leads to intrapartum fever. It was reported that ELA-related maternal fever is associated with inflammation; however, whether it is of infectious origin remains unclear.^[57-60] Third, systemically administered opioids (in women without ELA) suppress the development of maternal fever^[61]; but conflicting evidences also exist.^[48,61,62]

Maternal fever is associated with worse neonatal outcomes. Neonates of women with intrapartum fever are

more likely to have a low Apgar score and neonatal morbidity (such as asphyxia, seizure, and sepsis), and require more resuscitation or cardiopulmonary resuscitation and NICU admission.^[63-69] In addition, maternal fever may be associated with higher risks of cognitive deficit and cerebral palsy in early childhood.^[70,71]

Since ELA increases the risk of intrapartum fever and the latter is associated with adverse neonatal sequelae, it is possible that ELA may produce harmful effects on neonates by increasing maternal temperature. Indeed, in an observational study of low-risk women receiving ELA, it was found that intrapartum maternal fever (>37.5°C) was associated with adverse neonatal outcomes, and there was a significant linear trend between maximum maternal temperature and overall neonatal outcomes.^[72] In a population-based registry study, Törnell *et al*^[73] reported that the use of ELA was associated with a lower Apgar score (<7 at 5 min), but not the risk of neonatal encephalopathy; whereas maternal fever was associated with both adverse outcomes.

ELA, Instrumental Delivery, and Children’s Long-term Outcomes

When compared with parenteral opioid analgesia, neuraxial labor analgesia does not increase the rate of Cesarean delivery but increases the likelihood of instrumental delivery.^[34,74] When comparing early *vs.* late ELA, there were no significant differences regarding the risks of Cesarean delivery or instrumental vaginal delivery.^[75] The ELA-related increase of instrumental delivery raises the concern about the risk of birth injuries. Indeed, studies reported that instrumental vaginal delivery is responsible for most cases of neonatal birth trauma, including head injuries.^[76-78] It is suggested that only practitioners who are adequately trained or under supervision should undertake instrumental delivery.^[77]

Several studies investigated the long-term outcomes of children after instrumental delivery. In an early retrospective cohort study of 52,282 children, an intelligence test and medical examination were done at 17 years of age. After adjustment for confounding factors, the mean intelligence scores did not differ among those after vacuum, forceps, and spontaneous delivery. Although children after forceps or vacuum delivery had functional impairment when compared with those after spontaneous delivery, the differences were small. The authors concluded that the vacuum and forceps deliveries do not increase the long-term physical and cognitive impairment.^[79] In a later prospective cohort study, 393 children were followed up at 5 years after operative (instrument vaginal or cesarean) delivery. The results also showed that the rates of neurodevelopmental morbidity were low and comparable between groups.^[80]

Considering the available evidences, ELA may increase the rate of instrumental delivery and birth trauma, but does not produce significant adverse effects on long-term outcomes of children. Measures to reduce instrumental delivery during ELA are still worthy of further attention.

ELA, Postpartum Depression, and Children’s Neurodevelopment

Postpartum depression is a common psychological complication associated with childbirth and occurs in approximately 10% to 20% of new mothers.^[81-84] It is an important public health issue, because it affects not only the mental health of mothers themselves but also the cognitive and emotional development of their children.^[83,85-88] As revealed in a systematic review, the majority of available studies reported that mothers’ postnatal depression is associated with a worse cognitive development in later childhood.^[89] These findings suggest that prevention of postpartum depression is a potential strategy to optimize toddlers’ cognitive development [Figure 1].

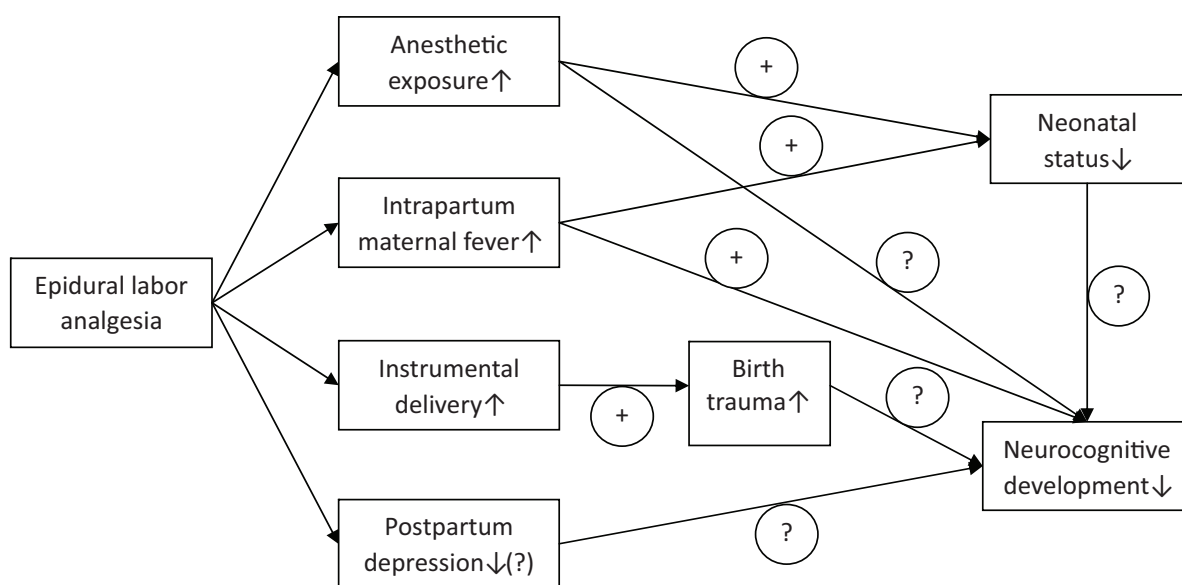


Figure 1: Summary of the potential impact of epidural labor analgesia on the outcomes of neonates and children. ↑ means increase; ↓ means decrease or deterioration; ⊕ means positive effect, that is, increase the outcome; ⊕ means the effects are unclear.

Multiple factors have been identified to be responsible for the development of postpartum depression, including previous maternal blues/psychiatric illnesses, negative attitude during pregnancy, stressful life events, poor marital satisfaction, and lack of social support.^[84] Furthermore, intense pain during labor is also an important risk factor. In a multicenter prospective cohort study, Eisenach *et al*^[90] found that the severity of acute pain after childbirth predicted the development of postpartum depression.

Multiple interventions (including biological and psychological/psychosocial interventions) have been studied to prevent the occurrence of postpartum depression.^[81] Besides, effective labor analgesia may also be promising. In an early study, Hiltunen *et al*^[91] reported that pain relief during vaginal delivery decreased the depression score immediately postpartum, but not that 4 months later. In a prospective cohort study of 214 primiparae, Ding *et al*^[17] found that the use of ELA was associated with a lower risk of postpartum depression at 6 weeks. Similar results were also reported by Suhitharan *et al*^[18] in a case-controlled study, that is, the absence of ELA was an independent risk factor for the development of postpartum depression. Furthermore, a recent study of Liu *et al*^[19] showed that the use of neuraxial analgesia during labor was associated with a reduced risk of maternal depression at 2 years after childbirth.

Considering the negative impacts of maternal depression on children's neurocognitive development, it is possible that the use of ELA may improve children's neurodevelopment by decreasing postpartum depression and even long-term depression after childbirth. However, evidences in this aspect are still lacking and further studies are required.

Conclusions

The anesthetics (especially opioids) administered during ELA can be absorbed and produce neonatal depression; however, this effect is less severe than systematic opioids. The impacts of anesthetic exposure during ELA on children's neurodevelopment have not been studied sufficiently but would be mild if any. ELA increases the risk of intrapartum fever, which may produce harmful effects on neonates. ELA may increase neonatal injury by increasing instrumental delivery, although long-term adverse outcomes are rare. On the other hand, ELA may have favorable effects on children's neurocognitive development by decreasing maternal depression; but evidences are still lacking. The overall impact of ELA on neonatal and children's outcomes deserves further study.

Conflicts of interest

None.

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