



Labor neuraxial analgesia and clinical outcomes

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Labor neuraxial analgesia (LNA) is a gold standard for managing labor pain in the modern world. It provides better and safer analgesia than other pharmacological labor pain relief [1]. However, reducing labor pain by the technique must be balanced considering clinical outcomes because inappropriate analgesia negatively impacts both mothers and babies. For considering maternal-centered LNA, clinicians should take into consideration four types of clinical outcomes: obstetrical (e.g., operative delivery rate, length of labor), maternal (e.g., fever, hypotension, adverse effects related to neuraxial medications), fetal (e.g., heart rate tracing, abnormal deceleration), and neonatal (e.g., a requirement of resuscitation, neonatal intensive care unit admission) (Table 1). Of note, as LNA is getting popular worldwide, clinical interests for both healthcare providers and consumers, such as mothers and their families, have expanded with broad consequences.

When LNA was introduced into clinical practice, we had great discussions, mainly on obstetrical outcomes. For instance, some clinicians initially believed that reducing labor pain by LNA increased cesarean delivery rate [1, 2]; LNA induced maternal fever, well known as ‘epidural fever,’ which was thought to result from intrauterine infection [3]; prolonged labor by LNA increased incidence of postpartum hemorrhage [4]. All these myths have been resolved by dedicated obstetric anesthesiologists worldwide. LNA in the early days did increase the cesarean delivery rate. Classical LNA consumed semi-surgical concentrated local anesthetics (bupivacaine 0.25% or ropivacaine 0.3%) for maintaining labor analgesia and produced motor blockade during labor, which interfered pushing in the second stage of labor, resulting in failure to progress and cesarean section. Obstetric anesthesiologists reduced the concentration

by keeping appropriate labor pain relief by a supplemental neuraxial opioid to overcome the negative result. After applying low concentrated local anesthetics with a small dose of lipophilic opioids, such as fentanyl or sufentanil, modern parturients have not experienced a higher incidence of intrapartum cesarean delivery under LNA [1]. Another myth we struggled with was epidural fever. Women having LNA indeed tend to develop pyrexia beyond 38°C. Obstetricians in the old days believed the epidural fever was related to chorioamnionitis, and when mothers had a fever, they occasionally asked anesthesiologists to discontinue the epidural analgesia. The mechanism of epidural fever is not fully understood, but we found that several inflammatory cytokines increase under LNA [5]; the origin is not considered an infection in our current practice. Although we are very sensitive to fever during the COVID-19 pandemic, authorities recommend considering LNA for labor management to avoid urgent general anesthesia [6]. Some Japanese obstetricians have concerns that LNA increases postpartum hemorrhage because there is evidence of LNA related to a longer delivery process than systemic analgesia, which can induce uterine atony by exhausting the myometrium and higher instrumental delivery rate. Research of uterotonics for appropriate postpartum uterine contraction has revealed that one of the uterine atonies after prolonged labor was influenced by the desensitization of oxytocin receptors [7]; so far, there is no solid evidence that LNA is associated with postpartum hemorrhage. Instead, LNA would prevent postpartum hemorrhage by early deteriorating vital signs after minimal blood loss due to the sympathetic block and allowing clinicians to intervene in fluid resuscitation in an early stage of bleeding. Also, the newly developed LNA maintenance technique, programmed intermittent epidural bolus, may potentially solve an issue of higher incidence of instrumental delivery [8]. Furthermore, from the point of view of obstetricians, when they find the bleeding and the parturient is well anesthetized, it allows them to perform hemostatic maneuvers without hesitation, such as bimanual uterine compression, laceration repair, manual removal of placenta, or intrauterine tamponade. The quick responses

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Table 1 Clinical outcomes associated with labor neuraxial analgesia

Obstetrical	Length of labor (e.g., first and second stage of labor) Mode of delivery (e.g., spontaneous vaginal, instrumental, cesarean) Labor augmentation Oxytocin dosage Uterine hypertonus Labor pattern (e.g., prolongation, protraction, arrest) Birth canal laceration/obstetrical and sphincter injuries (OASIS) Episiotomy Position/presentation (e.g., occiput posterior position, face presentation) Dystocia Chorioamnionitis/meconium staining Retained placenta Postpartum hemorrhage/transfusion/peripartum hysterectomy
Maternal	Hypotension (with or without pharmacological interventions) Fever Pruritus Nausea and vomiting Quality of analgesia (e.g., pain scores, breakthrough pain, additional analgesia bolus, number of patient-controlled epidural analgesia boluses) Local anesthetic/opioid consumption Motor block (e.g., modified Bromage scale) Epidural replacement Respiratory depression/sedation Adverse events (e.g., accidental dural puncture, postdural puncture headache, high neuraxial block, local anesthetic systemic toxicity, aspiration, unrecognized catheter migration) Mental health (e.g., postpartum depression, post-traumatic stress disorder) Postpartum complication (e.g., pain, anemia)
Fetal	Fetal heart rate tracing (e.g., baseline heart rate, variability, acceleration, deceleration, fetal bradycardia, sinusoidal pattern) Intrauterine fetal resuscitation (e.g., oxygen supplementation, left uterine displacement, fluid bolus) Scalp stimulation Umbilical blood gas (e.g., pH, PCO ₂ , PO ₂ , SO ₂ , base excess, lactate)
Neonatal	Apgar scores Birth size (e.g., weight, height, head circumference) Acute injury related to delivery (e.g., cephalohematoma, subgaleal hemorrhage, brachial plexus injury, clavicular fracture) Neonatal resuscitation (e.g., continuous positive airway pressure, subglottic airway, endotracheal intubation) Neonatal intensive care Pulmonary surfactant/bronchopulmonary dysplasia (BPD) Mechanical ventilation/non-invasive ventilation Hypoglycemia Transient tachypnea of newborn (TTN) Intracranial hemorrhage (ICH)/periventricular leukomalacia (PVL) Sepsis/necrotizing enterocolitis (NEC) Retinopathy of prematurity (ROP) Cerebral palsy Anemia/transfusion Neurological outcomes (e.g., neurodevelopmental impairment, autism spectrum disorder)

would reduce the severity of the imminent situation, but we are conducting reliable and scientific research to connect missing chains. In these manners, obstetric anesthesiologists have contributed to investigating the relationship between LNA and clinical outcomes.

Even though clinical benefits of managing labor pain by LNA are obvious, and negative impacts on obstetrical and maternal outcomes are acceptable or almost negligible in modern medicine, recent big data analyses fuel the debate in the obstetric anesthesia community. In October 2020, Qiu et al. reported that offspring from mothers having LNA had a higher incidence of autism spectrum disorders (ASD) [9].

The paper was published in the *JAMA Pediatrics*, one of the world's leading academic journals in pediatrics, which led to massive conflicts and discussions in anesthesia, obstetric and pediatric academies. Immediately after the publication, the Joint Statement by the Society for Obstetric Anesthesia and Perinatology, the American Society for Anesthesiologists, the Society for Pediatric Anesthesia, the American College of Obstetricians and Gynecologists, and the Society for Maternal–Fetal Medicine was circulated and announced that “Labor Epidurals Do Not Cause Autism” [10]. Also, 17 researchers posted direct comments in the journal. Eventually, Wall-Wieler et al. conducted a counter research with

the negative association of LNA and ASD and published it in the same journal in April 2021 [11]. The discussion is expanding. In September 2021, two big data analyses with conflicting results of the association between labor epidurals and autism were published in the *JAMA* [12, 13], attached with the elegant editorial by Wong and Stevens [14]. Of note, the pathogenesis of ASD remains unclear. Still, genetic components could play an essential role in triggering the condition. Most big data analyses for ASD related to childbirth events include only maternal genetics. Half of the neonatal genetic information comes from the paternal side; thus, we need more extensive and decent research, including father information, to unlock the causality.

On the other hand, LNA could have positive results in maternal mental health. As maternal death related to postpartum depression has been a massive issue in Japan and other countries, this impact would not be negligible. Same as the association above, we only have mixed results in the realm at this moment [15]. Similarly, some researchers suggest the correlation between providing LNA and increasing successful breastfeeding. Although LNA must alter the parturient experience of childbirth events compared to natural birth without pharmacological analgesia, we should recognize that it is not reasonable that a single intervention leads to a pathologic condition with multiple causalities. Big data analyses are not the magic wand to solve the clinical association between childbirth events and long-term maternal and neonatal outcomes. Our practice would never be perfect, and we must investigate new scientific methodology and conduct clinically reliable research for future mothers and babies.

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