

Effects of Epidural Analgesia on Fetal Well-Being

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The use of epidural analgesia has gained popularity among both obstetricians and parturients in China. Appropriate use of an epidural test dose and fractionation of large epidural doses of local anesthetics have made epidural anesthesia a very safe modality for the expecting mother and her fetus.

Meticulous attention to techniques as well as constant vigilance to avoid preventable errors allow the anesthesiologist to administrate **safe** labor analgesia and to insure maternal, fetal and neonatal well-being. Adverse effects of epidural analgesia on the fetus can originate **directly** from the drugs used (local anesthetics and opioids) or **indirectly** from maternal hemodynamic changes due to loss of vasomotor tone from the sympathetic blockade of the epidural. The aim of this review is to highlight the influence of epidural analgesia on fetal and neonatal outcomes and to outline our understanding on placental drug transfer, uteroplacental blood-flow and acid-base balance and their impact on neonatal outcome.

1. Epidural opioids and neonatal respiratory depression

Fentanyl and sufentanil are widely used for labor epidural analgesia. Both are highly lipophilic and able to cross placenta into fetal circulation. Following administration of 100 µg of fentanyl into the epidural space, a significant amount of fentanyl rapidly crosses the placenta with a fetal/maternal blood concentration ratio of 0.89 [1]. Therefore, fentanyl poses a potential for producing neonatal respiratory depression. Sporadic case reports have documented such neonatal respiratory depression that has been reversed by naloxone injection intramuscularly [2]. In contrast, in vitro placenta perfusion studies have shown that sufentanil has lower placental transfer due to high levels of protein binding in maternal circulation [3, 4]. These studies appear to suggest that sufentanil could be the opioid of choice for epidural analgesia. It has been observed in multiple studies there exists a synergy between local anesthetics and opioids that will significantly improve analgesia and decrease the total opioid requirement, therefore, increase the safety of using opioids in parturients. Also, it is wise to avoid bolus of fentanyl and sufentanil if delivery is imminent in 45 minutes. Availability of naloxone near by the newborn baby warmer is highly recommended in case of neonatal respiratory depression.

2. Intrathecal opioids and fetal heart rate abnormality

The effect of intrathecal opioids on fetal heart rate (FHR) has remained a controversial topic in obstetric anesthesia. Abnormal FHR patterns such as late decelerations and fetal bradycardia have been reported after administration of epidural or combined spinal and epidural analgesia, especially when high dose of opioids were used. Van de Velde and colleagues reported that, in a randomized, double-blinded trial, intrathecal sufentanil in a dose of 7.5 µg is associated with 2 fold higher incidence of non-reassuring FHR patters and slightly higher Cesarean section rate when compared to the group received the same dose of sufentanil by epidural [5]. However, despite the

increased frequency of FHR abnormalities, the neonatal outcomes were favorable in all groups. There was no emergency Cesarean deliveries needed as a result of non-reassuring FHR tracing. The epidural fentanyl had similar effects on FHR, but with lower incidence compared to sufentanil [6]. The presumed mechanism of opioid-induced FHR abnormality is due to uterine hyperactivity that decreases utero-placental blood flow. It has been postulated that the uterine hyperactivity is caused by rapid onset of analgesia, leading to a significant decrease in maternal circulating catecholamine levels. It is highly recommended to utilize the synergistic effect of the combination of local anesthetics and opioids to reduce the dose of narcotics needed and ultimately minimizing adverse side effects.

3. Placental transfer of local anesthetics and effect of fetal “ion trapping”

Local anesthetics are weak bases that can cross the placenta in the non-ionized form only. Bupivacaine is the most widely used local anesthetic in obstetrical analgesia because of its safety profile for mothers and fetus. Bupivacaine crosses the placenta and its fetal/maternal ratio varies between 0.2-0.4 because it is highly (96%) bound to maternal glycoproteins. Neonatal exposure to bupivacaine clearly rises with the duration of epidural administration. Despite clear evidence of placental transfer, there are no reported adverse neonatal outcomes.

Lidocaine is frequently chosen for epidural anesthesia for Cesarean delivery due to its rapid onset when compared to bupivacaine. Lidocaine also traverses the placental barrier at a fetal/maternal ratio of 0.5-0.7. Repeated epidural injection of large dose of lidocaine during Cesarean section may result in a greater accumulation of the drug in newborn, however, any reported effects on newborns have been subtle and are probably not clinically significant because the term fetus is able to biotransform lidocaine by hepatic enzymatic activity and make it safe for the fetus.

The use of mepivacaine in obstetric epidural anesthesia fell into disfavor after an investigation demonstrated that mepivacaine crossed the placenta leading to higher concentrations in sampled cord blood (36-47% higher) than lidocaine. Furthermore, the elimination time in newborns of mepivacaine was found to be 9 hrs, three times longer than lidocaine [7]. In a rare case report, mepivacaine had been accidentally injected into the fetus in 4 cases following attempts to place a caudal epidural during labor, leading to intoxication of fetus. All infants were depressed and had convulsions, and two died soon after [8]. Currently, a caudal epidural for labor analgesia is not recommended.

For the amide local anesthetics, their pKa values are close enough to maternal physiologic pH leading to a considerable proportion of them in the non-ionized form in the maternal circulation and hence making them lipophilic and affording them the ability to cross the placenta into fetal circulation. In the acidotic fetus (pH<7.2), a greater proportion of drug is then converted into the ionized form and is unable across the placenta to be transferred back to the maternal circulation. It results in a larger amount of local anesthetic in fetal plasma, so called “ion trapping”. However, the toxic dose of local anesthetics in the newborn appears to be similar to that in the adult. The large volume of distribution and placenta barrier in the fetus are most likely responsible for the high dose of local anesthetic required to produce toxic effect.

Chloroprocaine has gained popularity in the United States, especially for emergency Cesarean sections. Rapid hydrolysis by plasma cholinesterase in the mother and neonate with normal enzyme levels limit its potential for toxicity.

Abboud and colleagues [9] studied the effects of epidural anesthesia on newborn outcomes in 54 pregnant women undergoing Cesarean section. In this study, epidural injections of bupivacaine, lidocaine and chloroprocaine for Cesarean sections had no adverse effect on the newborns' Apgar scores, cord acid-base status, or the early neonatal neurobehavioral scale.

Newer amide local anesthetics, such as ropivacaine and levobupivacaine, feature the beneficial blocking properties and lower potential for cardiotoxicity. From limited data, it is generally perceived that the safety profiles for the fetus of these drugs are similar to that of bupivacaine.

4. Epidural/combined spinal and epidural anesthesia induced maternal hypotension and umbilical cord base-acid status

It must keep in mind that drugs may affect the baby in two ways: via a direct effect, resulting from placental drug transfer as well as an indirect effect, resulting from maternal physiological or hemodynamic changes.

Hypotension related to labor epidural and combined spinal/epidural is mostly mild but can be severe when epidural analgesia is attempted for Cesarean section. The reported incidence of maternal hypotension varies between 5-50% [10]. The strategies to prevent hypotension include left uterine displacement, intravenous fluid hydration and early vasopressor administration. It seemed initially that ephedrine was the logical vasopressor of choice for maternal hypotension due to both alpha and beta sympathomimetic effects making it ideal protection for placental blood flow. This was supported by not only animal but also human studies [11]. Therefore, historically, ephedrine was used as the main vasopressor. Despite wide acceptance, its superiority over other vasopressors has not been clearly defined. Recently, studies comparing ephedrine and phenylephrine showed the risk of true fetal acidosis (umbilical arterial pH <7.20) was higher in the ephedrine group [12]. However, there is no difference in fetal outcome measured by Apgar scores. Ephedrine-induced beta-adrenergic stimulation of the fetus is a possible mechanism of fetal acidemia resulting from increased oxygen consumption and lactic acid production. The clinical significance of lower umbilical cord pH is not clear. Phenylephrine can be safely used to manage maternal hypotension and may be used even as first line treatment.

Inadvertent subarachnoid injection of a large dose of epidural local anesthetics can cause total or high spinal. Severe maternal hypotension can have detrimental effects on the fetus as well. Prompt diagnosis and resuscitation should prevent maternal mortality and intrauterine fetal asphyxia.

In summary, epidural analgesia is safe for both parturient and her fetus, and therefore, it has been used successfully to support the natural process of labor.