Threshold of metabolic acidosis associated with newborn cerebral palsy: medical legal implications

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Obstetricians and gynecologists belong to 1 of the medical specialties with the highest rate of litigation claims. Among birth injury cases, those cases with cerebral palsy outcomes account for litigation settlements or judgments often in the millions of dollars. In cases of potential perinatal asphyxia, a threshold level of metabolic acidosis (base deficit ≥12 mmol/L) is necessary to attribute neonatal encephalopathy to an intrapartum hypoxic event. With increasing duration or severity of a hypoxic stress resulting in metabolic acidosis, newborn infant umbilical artery base deficit increases. It may be alleged that, as base deficit levels increase beyond 12 mmol/L, there is an increased likelihood and severity of cerebral palsy. As a corollary, it may be claimed that an earlier delivery (by minutes) would reduce the base deficit and prevent or reduce the severity of cerebral palsy. This issue is of relevance to obstetricians as defendants, because retrospective "expert" analysis of cases may suggest that optimal management decisions would have resulted in an earlier delivery. In addressing the association of metabolic acidosis and cerebral palsy, base deficit should be measured as the extracellular component (base deficit$_{extracellular\ fluid}$) rather than the commonly used base deficit$_{blood}$. Studies suggest that, beyond the base deficit threshold of 12 mmol/L, the incidence and severity of cerebral palsy does not significantly increase (until ≥20 mmol/L), although the risk of neonatal death rises markedly. Thus, among most infants with hypoxia-associated neonatal encephalopathy, the occurrence of cerebral palsy is unlikely to be impacted by delivery time variation of few minutes, and this argument should not serve as the basis for medical legal claims.

Key words: acidosis, base deficit, brain injury, cerebral palsy, encephalopathy, hypoxia

Among the medical specialties, obstetricians and gynecologists have among the highest average indemnity payments and paid-to-closed ratios.[1,2] Nearly 75% of physicians who practice obstetrics and gynecology will encounter a malpractice claim by age 45.[3] Within obstetrics, the highest litigation claims are associated with cerebral palsy, because the life care plans for these children average over 1 million dollars[4,5] and medical legal settlements and judgments often far exceed this cost.

The consequences of obstetric malpractice litigation include the dramatic increase in the cesarean delivery rate,[6] the rise in malpractice premiums,[7] and the loss of obstetric practitioners.[8] The challenges of cerebral palsy litigation have been well-described,[9] including nonhypoxic causes for neonatal encephalopathy,[10] limitations of electronic fetal monitoring,[11] patterns of plaintiff expert witnesses,[12] and introduction of "junk science."[13] Several of these issues are being addressed. The American College of Obstetricians and Gynecologists has issued guidelines for electronic fetal monitoring assessment,[14] and recent studies have provided insight for labor management guidance,[15–17] with evidence that a potential reduction in the cesarean delivery rate can be achieved without an increase in adverse neonatal outcomes.[18] Several states have incorporated no-fault, medical malpractice liability for common insurance,[19,20] although this has not been implemented widely.

Hypoxia-associated neonatal encephalopathy and cerebral palsy: base deficit threshold

There are often contentious medical-legal debates as to whether a hypoxia-associated neurologic injury occurred during labor and delivery and, if so, was it preventable. The putative factor that is associated with fetal hypoxic-ischemic brain injury is metabolic acidosis. For cerebral palsy to be consistent with an acute peripartum or intrapartum asphyxial event, a threshold level of metabolic acidosis (base deficit [BD], ≥12 mmol/L) or mixed respiratory and metabolic acidosis pH (<7.0) has been accepted by the American College of Obstetricians and Gynecologists[21] based on both case-control and cohort populations[22] and endorsed by numerous international organizations that include the Australian Collaborative Cerebral Palsy Research Group, Japan Society of Obstetrics and Gynecology, and the Royal College of Obstetricians and Gynecologists, among others.

In medical legal liability cases, it is often alleged that a delay in delivery resulted in increased newborn infant metabolic acidosis.[23,24] Accordingly, it may be claimed that earlier delivery saving minutes of hypoxia would have reduced the level of acidosis and prevented newborn infant brain injury. Under this hypothetical, the umbilical artery BD may be reduced but remains above the threshold value of 12 mmol/L. This review will examine the scientific and medical evidence as to whether the rate of cerebral palsy correlates with BD values at >12 mmol/L.

Causes of cerebral palsy

Averaging 2 per 1000 live births, the rates of cerebral palsy have not changed

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significantly when carefully assessed (eg, Sweden) since the early 1970s.[25] The most common types of cerebral palsy are spastic hemiplegia and diplegia (manifest as muscle spasticity on one side or both sides of the body, respectively), which are often associated with damage to the motor cortex and the pyramidal tracts. Dyskinetic cerebral palsy (manifest with movements that include dystonia, athetosis, and chorea) is often associated with basal ganglia damage and represents only 10−15% of cerebral palsy cases.[25] Epidemiologic studies indicate that only a small proportion of cerebral palsy (eg, 10−20%) is due to birth asphyxia.[26] In a report from Sweden, the cause of cerebral palsy was considered prenatal in 38%, peri/neonatal in 38%, and unclassified in 24%. Of the term peri/neonatal cases, "hypoxic ischemic encephalopathy" accounted for 34% of causes[25] and thus 13% of the total cases. Among a cohort of spastic cerebral palsy cases from Western Australia only 8% of cases were attributed to intrapartum asphyxia,[27] although a recent review of 23 studies confirmed the challenges of defining the precise association, because the proportion of cerebral palsy with birth asphyxia as a precursor varied from <3% to >50%.[28]

Although birth asphyxia-induced cerebral palsy has been associated with neonatal encephalopathy, alternative disorders that include brain malformations, fetal growth restriction, and placental diseases may manifest as neonatal encephalopathy. Furthermore, prematurity,[29,30] perinatal infections, prelabor hypoxic events, perinatal stroke,[31] congenital or metabolic abnormalities, and neonatal hypoxia or hypoglycemia may or may not exhibit neonatal encephalopathy.[32] Thus, it is often challenging to definitively assign a hypoxia-associated cause for neonatal encephalopathy.

Retrospective review of medical care

The assessment of medical care, whether performed for quality improvement or medical legal purposes, is by default a retrospective analysis. Retrospective case reviews may introduce a lack of objectivity that is dependent, in part, on the outcome.[33] In retrospective assessments, "hindsight bias" is the tendency for people with knowledge of the actual outcome of an event to believe falsely that they would have predicted the outcome.[34,35] Accordingly, hindsight bias may cause an expert to simplify, trivialize, and criticize retrospectively the decisions of a treating doctor.[36] Optimally, clinician decisions must be judged prospectively with the understanding that a compendium of symptoms, signs, or findings may represent multiple diagnoses, care paths, and outcomes.

Within obstetrics, a majority of medical legal claims are based on presumption of substandard care during labor and misinterpretation of fetal heart tracings.[37] More than one-half of obstetric claims from the United Kingdom and Hong Kong (1984−1994) were assessed as misguided allegations,[23] which emphasizes the importance of unbiased expert assessment. Further challenging the process of retrospective obstetric case reviews is that expert intra- and interobserver variability of fetal heart tracing interpretation has been quantified as mediocre and poor, respectively.[38] In obstetric malpractice cases, hindsight analysis may determine that a decision for cesarean delivery, often based on interpretation of fetal heart tracings, should have occurred before that which was actually performed, resulting in earlier delivery of an infant. Despite these concerns for unbiased review and potential hindsight bias, is there scientific evidence for reduced metabolic acidosis and prevention of cerebral palsy in a delivery performed minutes earlier?

Correct measure of metabolic acidosis: $BD_{extracellular\ fluid}$

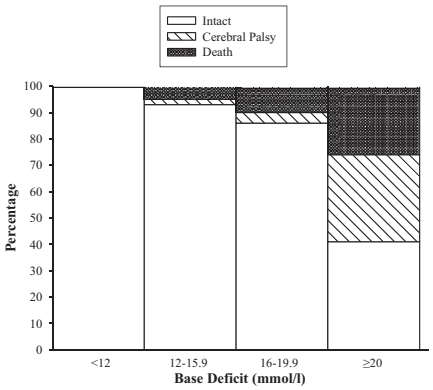
The quantification of umbilical cord acid base status requires appropriate sampling and measurement. Sampling should be performed from double-clamped cord segments or direct puncture of the umbilical artery and vein at delivery and, ideally, stored in glass syringes to prevent gas diffusion through plastic syringes,[39] and analysis should be performed within 30 minutes.[40] Optimally, cord artery assessment of metabolic acidosis should include both umbilical artery and vein samples to ensure that artery samples were identified accurately.[41] BD calculations, which are derived from pH and P_{CO_2} values, should include the whole of the extracellular compartment, based on Siggaard-Andersen Acid-Base Chart algorithms,[42] which are incorporated into some, although not all, commercial blood gas analyzers. Recent publications have emphasized that $BD_{extracellular\ fluid}$ (BD_{ECF}; isocapnic) rather than BD_{blood} represents the appropriate assessment of the degree of metabolic acidosis.[43] In the presence of elevated P_{CO_2} levels, BD_{blood} will be inappropriately quantified as a higher number than $BD_{ECF,}$ with increasing differences with greater P_{CO_2} levels. Because an umbilical artery P_{CO_2} can exceed 100 mm Hg with bradycardia, these differences may be marked. Increased CO_2 results in respiratory acidosis in the following manner: $CO_2+H_2O \leftarrow \rightarrow H_2CO_3 \leftarrow \rightarrow H^+ + HCO_3^-$. Because HCO_3^- leaves the intravascular space to enter the expanded extracellular compartment, the remaining H+ "falsely" lowers the pH and increases the calculated BD_{blood}. The calculation of BD_{ECF} accounts for this process and provides an accurate measure of the metabolic component of acidosis.

The accurate assessment of metabolic acidosis can be critical to the interpretation of obstetric practice and newborn infant treatment. Because BD_{ECF} is a calculated value, the modification of hospital clinical laboratory and manufacturer's blood gas analyzer software to include this measure is a simple action that can improve acidosis assessment.

How rapidly does the fetus develop metabolic acidosis?

To determine the impact of "minutes saved" from an earlier delivery, one must assess the rates of fetal BD change. The normal fetus in utero has an umbilical artery BD of 1−2 mmol/L,[44,45] which increases to approximately 5 mmol/L[46] after a vaginal delivery, which is a result of the normal hypoxic stress that is associated with uterine contractions and

FIGURE
Graphic representation



The graph shows the rates on intact survival, cerebral palsy, and death at 2 years of age by level of base deficit.[55] Note that the rate of death, although not cerebral palsy, increases from 12−15.9 to 16−19.9 mmol/L.

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common fetal heart rate decelerations. Studies in ovine fetal models provide quantitative measures of the effect of fetal heart rate decelerations on BD. Mild, moderate, and severe variable decelerations increase BD by approximately 0.2, 0.25, and 0.5 mmol/L per minute of deceleration, respectively.[47,48] Based on human studies, prolonged decelerations or bradycardia (50−70 beats/min) have an effect equivalent to severe variable decelerations in the ovine model, which results in a BD increase of 0.5 mmol/L per minute.[49,50] Additional fetal heart rate patterns that include sinusoidal[51] and prolonged saltatory[52] heart rates have been associated with metabolic acidosis, although the rates of BD increase are not known. During recovery between fetal heart rate decelerations, the placenta clears fetal metabolic acidosis at approximately 0.1 mmol/L per minute.[47,48] Thus, the net effect of a postulated earlier delivery on umbilical artery can be calculated.[47,48,53,54]

Does an increase in BD predict increased rate of cerebral palsy?

Among near-term or term infants (≥35 weeks gestation) with admission to the neonatal unit and marked acidosis (BD 12 mmol/L or pH <7.0), 196 of 223 infants (88%) had a BD value between 12 and 20 mmol/L.[55] Accordingly, a delivery that occurs a few minutes earlier would, in most cases, still project the umbilical artery or early newborn infant BD to exceed 12 mmol/L. The question is postulated as to whether this would result in the prevention of cerebral palsy or reduction of injury, assuming that umbilical artery BD remains in range of 12−20 mmol/L.

Epidemiologic studies support the conclusion that increased BD beyond the threshold of 12 mmol/L (up to 20 mmol/L) is not associated with more frequent or more severe cerebral palsy. Freeman and Nelson[56] concluded there was no association of the degree of pH, BD (>12 mmol/L), or other measures of fetal oxygenation with long-term neurologic outcome. A recent, large retrospective cohort review of the association of umbilical BD with neurodevelopmental outcome demonstrated no significant increase in the rate of cerebral palsy among infants with acidosis at birth (umbilical cord or blood sample within the first hour of life), comparing BD values of 12 to <16 mmol/L vs 16 to <20 mmol/L.[55] Among infants with a BD of 12−15.9 mmol/L, the rate of cerebral palsy was 2.1%, which did not increase significantly (4.0%) among those with BD 16−19.9 mmol/L. In contrast, there was a marked increase (33%) in the rate of cerebral palsy at >20 mmol/L. Although the majority of survivors at any BD level did not exhibit cerebral palsy, the rate of death (up to 2 years of age) increased from 5% at BD 12−15.9 mmol/L, to 10% at 16−19.9 mmol/L, to 26% at BD ≥20 mmol/L (Figure). The authors acknowledge that the extent to which acidosis predicted cerebral palsy may be overestimated, because only 5.1% of eligible infants had BD measured. Furthermore, the authors do not detail whether BD_{blood} or BD_{ECF} was determined. Similarly, a study with a smaller sample size (n=35) demonstrated that BD ≥20 mmol/L was highly predictive of death or disability, with a positive predictive value of 93.8%.[57] There was a significant increase in the rate of death with BD ≥25 mmol/L, compared with BD ≥20 mmol/L, but no report of increased infant disability.

Studies that have reported scoring systems for the prediction of neonatal morbidity after acute perinatal asphyxia have not demonstrated a predictive value of increasing umbilical artery BD but rather use only the threshold BD.[57−60] In fact, several studies emphasize that the degree of fetal acidemia does not correlate with long-term neurodevelopmental sequela.[61−63] A recent metaanalysis of the strength of the association between umbilical cord acidosis and both perinatal and long-term outcomes[64] demonstrated that a low arterial cord pH (defined as <7.0−7.2) was associated with the development of cerebral palsy but failed to demonstrate any dose-response association of the degree of acidosis with the rate of occurrence or severity of cerebral palsy.

The majority of published studies have not differentiated umbilical artery BD_{blood} from BD_{ECF}. In an early study of asphyxiated infants, Low et al[49] reported that the mean umbilical artery and umbilical vein BD values (measured as buffer base) were not different between infants who exhibit cerebral symptoms and those with no cerebral symptoms. In a subsequent paper, Low et al[22] suggested that the rate of immediate newborn infant complications, including encephalopathy, increased from an umbilical artery BD of 8−12 mmol/L to >16 mmol/L, although these infants were followed only during the initial neonatal hospitalization. There was no accounting for infants who died in the early newborn period, because the report examined only complications among newborn infants who were alive at 5 days. Most importantly, this article compares outcomes to a previous report[65] of infants with an umbilical artery BD >16 mmol/L. However, as detailed within the referenced article,[65] the criteria of BD 16 mmol/L is equivalent to BD_{ECF} of 12 mmol/L and confirmed by analysis of the mean values in the metabolic acidotic group (pH 6.97, P_{CO_2} 78) which results in BD_{ECF} of 12 mmol/L. Thus, the comparison of the BD group of 12−16 mmol/L[22] with BD >16 mmol/L is actually a comparison of

BD_{ECF} <12 mmol/L to BD_{ECF} ≥12 mmol/L. Accordingly, it is not surprising that, in the BD_{ECF} <12 mmol/L group, there is only 1 case of severe central nervous system abnormality among 58 newborn infants (which perhaps represents a preexisting condition or alternative cause).

Why is increasing BD not associated with increased risk of cerebral palsy?

Physiologic studies that used animal models have contributed importantly to the understanding of hypoxic-ischemic cerebral injury. Among ovine, feline, or porcine fetuses that were exposed to prolonged marked hypoxia, brain damage occurred primarily in those that exhibited a significant reduction in mean arterial blood pressure.[66–69] Studies in rhesus monkeys confirm the hypoxia-associated decline in blood pressure with reductions in cardiac contractility and stroke volume, rather than reduced vascular resistance or inadequate venous return.[70] These studies emphasize the combined role of systemic hypoxemia/acidemia and cerebral ischemia as determinant factors for neurologic injury. The degree of hypoxia and/or ischemia that is necessary to produce permanent brain damage in the primate is close to that that is lethal,[56] which accounts for the increased rate of death, although not cerebral palsy, within the BD range of 12–20 mmol/L.[55] Unfortunately, electronic fetal monitoring has limited ability to assess fetal blood pressure or blood flow alterations that may contribute to cerebral injury.[71]

Local brain cellular effects (eg, inflammatory cytokines, excitatory neurologic signals), the potential for reoxygenation injury, and whole-body or head cooling of at-risk infants further contribute to the lack of association of increasing BD beyond 12 mmol/L with more frequent or more severe cerebral palsy. Hypothermic treatment has found promising results; a large randomized trial demonstrated a reduction in death or moderate-to-severe disability in near-term (>35 weeks gestation) or term infants with hypoxia-associated neonatal encephalopathy.[72] However, recent follow up of these infants to 6–7 years of age demonstrated a benefit limited to lower death rates and not severe disability.[73] Because hypothermia therapy is designed for infants with hypoxia-associated neonatal encephalopathy, it is increasingly important to identify those infants with neonatal encephalopathy who may benefit from the treatment.[72]

Nonhypoxia causes of cerebral palsy

The complexity of clinical factors that contribute to the absence of an association of BD with occurrence or severity of cerebral palsy (beyond the threshold level) include the gestational age of the newborn infant. Rates of cerebral palsy increase markedly with low birthweight and very low birthweight,[74] although most cases occur after term births.[25,29] The role of preterm intrauterine inflammation/infection remains controversial with studies that demonstrate a lack of association of inflammatory cytokines with cerebral palsy[75] but a significant association with neonatal periventricular leukomalacia, ventricular enlargement, and moderate/severe germinal matrix hemorrhage.[76] Studies of Yoon et al[77] have confirmed that preterm infants with elevated amniotic fluid or umbilical cord proinflammatory cytokines are at increased risk of periventricular leukomalacia, with animal studies that confirm the concordance of systemic and histologic evidence of inflammation in neonatal brains. Because periventricular leukomalacia may be a predecessor of cerebral palsy,[78] the prevention of perinatal infection that is related cerebral damage represents an opportunity for an impact on cerebral palsy consequences. Adding to the controversy, recent studies indicate an association of neonatal infection with cerebral palsy in term, although not preterm, infants.[79]

Fetal growth restriction is associated significantly with the development of cerebral palsy[80] with mechanisms postulated to include impaired maturation of oligodendrocytes that results in deficient myelination.[81] Optimal delivery timing and management of growth-restricted pregnancies remain controversial. However, neurodevelopmental outcomes possibly may be improved with delivery timing dependent on ductus venosus Doppler blood flow measures.[80,82]

Predictive value of Apgar scores for cerebral palsy

In contrast to BD, there is a significant association of longer durations of low Apgar scores (eg, 15 minutes) with increasing rates of cerebral palsy.[56] Among asphyxiated infants, a 10-minute Apgar score ≤3 is associated with a risk of cerebral palsy of 16.7%, which decreases to 4.7% if the Apgar score increases (>3) at 15 or 20 minutes. Further studies confirm the association of Apgar scores in asphyxiated newborn infants as a predictor of cerebral palsy. Similar to BD, among infants with APGAR scores of 0–3 at 1, 5, 10, or 15 minutes, the rate of death far exceeds the incidence of cerebral palsy, and the majority of survivors do not exhibit cerebral palsy.[83]

As a complement to the immediate newborn infant period, neurologic assessment at 1-year of age may be predictive of the development and severity of cerebral palsy in infants who exceed a threshold degree of metabolic acidosis.[84]

Conclusion

The current findings support a threshold of metabolic acidosis (BD_{ECF} 12 mmol/L), which places an infant at risk for the development of cerebral palsy, with little if any evidence of a change in the occurrence or severity of cerebral palsy within the range of BD_{ECF} 12–20 mmol/L. Consequently, an infant known to have experienced asphyxia-induced cerebral palsy can be assumed to have experienced the injury that resulted in cerebral palsy at such time that the BD_{ECF} equals or exceeds 12 mmol/L. Unless there is unbiased evidence that earlier delivery was indicated and that the projected newborn infant BD would have been <12 mmol/L, the infant's long-term neurologic course likely would not have been altered. The allegation that delivery should have occurred a few minutes earlier and thus would have prevented the occurrence or

reduced the severity of cerebral palsy must be scrutinized on several levels, which include the appropriate measure of BD, the potential hindsight bias of retrospective reviews, and the correct assessment of the impact on newborn infant BD and thus cerebral palsy. In the absence of medical and scientific validity, these cases should not serve as the basis of medical legal claims. ■

BOX

Clinicians should expedite deliveries when appropriate and indicated, recognizing diagnostic challenges and both maternal and fetal welfare. However, allegations that physician negligence delayed a delivery (by minutes) and increased the likelihood and/or severity of cerebral palsy are unsupported by scientific evidence for the majority of cases.

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