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Neonatal serial creatinine levels as an adjunct biomarker in timing of fetal neurologic injury

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ABSTRACT

Objective: To investigate the rise and clearance of newborn creatinine in perinatal asphyxia as an adjunct biomarker to support or refute allegations of acute intrapartum asphyxia.
Study design: In this retrospective chart review, newborns > 35 weeks gestational age were evaluated from closed medicolegal cases of confirmed perinatal asphyxia and reviewed for causation. Data collected included newborn demographic data, patterns of hypoxic ischemic encephalopathy, brain magnetic resonance imaging, Apgar scores, cord and initial newborn blood gases, and serial newborn creatinine levels during the first 96 h of life. Newborn serum creatinine values were collected at 0–12, 13–24, 25–48, and 49–96 h. Newborn brain magnetic resonance imaging was used to define 3 patterns of asphyxial injury: acute profound, partial prolonged, or Both.
Results: Two hundred and eleven cases of neonatal encephalopathy from multiple institutions were reviewed from 1987 to 2019 with only 76 cases having serial creatinine values during the first 96 h of life. A total of 187 creatinine values were collected. Partial prolonged and Both had significantly greater degree of metabolic acidosis in the first newborn arterial blood gas in comparison to acute profound. Acute profound and Both had significantly lower 5- and 10- minute Apgar scores in comparison to partial prolonged. Newborn creatinine values were stratified by asphyxial injury. Acute profound injury showed minimally elevated creatinine trends with rapid normalization. Partial prolonged and Both demonstrated higher creatinine trends with delayed normalization. Mean creatinine values were significantly different between the three types of asphyxial injuries within 13–24 h of life at the time when creatinine values peaked ($p = 0.01$).
Conclusion: Serial newborn serum creatinine levels taken within the first 96 h of life can provide objective data of timing and duration of perinatal asphyxia.

1. Introduction

Neonatal hypoxic ischemic encephalopathy (HIE) is a perinatal asphyxial event that leads to disturbed neurologic function in a newborn greater than > 35 weeks gestational age manifested by subnormal level of consciousness, seizures, difficulty with initiating and maintaining respiration, and depression of tone and reflexes. The incidence of neonatal HIE is estimated to be 1.5 per 1000 live births. The timing and duration at which perinatal asphyxia occurs is often a focus of intense scrutiny for parents, physicians, and medical litigators. With approximately 15–20% of cerebral palsy cases having origin in the immediate intrapartum period, more objective tests are needed to validate the more common remote insult [1–3].

Although acute catastrophic sentinel events such as placental abruption, uterine rupture, or cord prolapse are associated with a high risk of severe fetal hypoxia, these events are rare. Approximately 75% of cases of fetal hypoxia occur gradually as a result of uterine contractions and underlying abnormal placental development [4]. Other intrapartum risk factors such as oligohydramnios or remote maternal trauma can also predispose a fetus to asphyxial brain injury. Perinatal asphyxia can be categorized into three patterns of injury based on duration and severity of the injury called acute profound (AP), partial prolonged (PP), and

Abbreviations: HIE, Hypoxic ischemic encephalopathy; AP, Acute prolonged; PR, Partial prolonged; B, Both acute profound and partial prolonged; NRB's, Nucleated Red Blood Cells; LFT's, Liver Function Test; AKI, Acute Kidney Injury.

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combination of Both AP and PP (B) (Table 1) [5].

The fetal diving reflex occurs if placental blood flow is interrupted and ensures adequate perfusion of the adrenals, coronaries, and the brain at the expense of less vital organs including the kidney, liver, and bone marrow. Several fetal compensatory mechanisms contribute to the diving reflex. With prolonged uteroplacental compromise, non-vital organs such as the bone marrow, liver, and kidneys can be compromised, as demonstrated by elevated nucleated red blood cells (NRBCs), liver function tests (LFTs), and creatinine, respectively. With acute intrapartum asphyxia, the short duration of the diving reflex can minimize vascular compromise to the bone marrow, liver, and kidney with attenuated multiorgan failure [4].

Currently, no single biomarker value or imaging can precisely time an asphyxial event. We hypothesize that newborn creatinine, a marker for renal function, will demonstrate a distinct pattern of rise and clearance based on the type and duration of asphyxial injury. Serum creatinine remains the standard for identifying acute kidney injury. Other commonly drawn labs such as Blood Urea Nitrogen have little predictive value in newborn renal function [6]. In this study, we reviewed newborn serum creatinine trends within the first 96 h of life in confirmed HIE cases after perinatal asphyxia.

2. Methods

This is an institutional review board approved retrospective review protocol that evaluated 211 newborns from closed medicolegal cases of alleged intrapartum asphyxia gathered over a 32-year period (1987–2019) and reviewed by a neonatal expert (JKM) for causation. We collected data including newborn demographic data, patterns of HIE, brain magnetic resonance imaging (MRI) findings, Apgar scores, cord blood gases, initial newborn blood gases, and serial newborn serum creatinine levels during the first 96 h of life. The first newborn blood gases were all drawn within 4 h of birth. Data points were entered into an institutional review board approved de-identified secure electronic database.

Eligibility criteria included cases of perinatal asphyxia in newborns $>$ 35 weeks gestational age with brain MRI consistent with HIE (Table 1) [4]. Cases were excluded from the review if clinical evidence of other causes of neonatal encephalopathy including intracranial hemorrhage, meningitis, hypoglycemia, and kernicterus. In addition, any newborn with a congenitally diagnosed renal anomaly, as well as newborns born to a mother with renal failure were excluded.

Two hundred and eleven cases of alleged intrapartum asphyxia were reviewed. Over this 32- year period, 75% of cases were reviewed for defense and 25% for plaintiffs from 31 states in the United States of America. All cases reviewed were settled, dismissed, or went to trial. Of 211 cases, 135 were excluded due to absence of brain MRI, only a single creatinine value, or death prior to imaging. Seventy-six cases had serial creatinine values. A total of 187 newborn serum creatinine values were collected at four different time periods, 0–12, 13–24, 25–48, and 49–96 h of life.

Newborn brain MRI was used to define 3 types of perinatal insults: AP, PP, or B. The mechanism of perinatal insult was further supported by maternal history and fetal heart rate tracings as determined by the delivering obstetrician. Table 1 defines these patterns of intrauterine injury [7]. We feel that the development for the classification of fetal heart rate tracings into categories I-III after 2008 had no impact on our study [8].

3. Statistical methods

Clinical characteristics, blood gases, and Apgar scores are reported by asphyxial injury type as medians and interquartile ranges (IQR). Kruskal-Wallis test p-values are reported to evaluate whether predictors differ significantly by asphyxial injury type. A linear mixed effects regression model was used to estimate least square means of creatinine levels stratified by asphyxial injury at 0–12 h, 13–24 h, 25–48 h, and 49–96 h after birth. A random intercept was included to account for within-patient correlations. This model used a maximum likelihood estimation method, a Kenward-Roger approximation to correct the denominator degrees of freedom, and an unstructured covariance structure. Each least square mean creatinine estimate is reported with 95% confidence intervals (CI). F tests are used to assess the significance of the asphyxial injury fixed effect within each of the time frames.

4. Results

Of the 76 newborns in this study, 22 (29%) had an acute profound injury, 22 (29%) had a partial prolonged injury, and 32 (42%) had Both. Not all newborns had every parameter (newborn creatinine, cord and first newborn blood gas, 10 min Apgar scores) available in their chart for analysis. Total number of cases (n) in each parameter subdivided by asphyxial injury are noted in Table 2. The overall median gestational age for the 76 newborns was 39 weeks (IQR 38–40) and median birth weight was 3300 g (IQR 2925–3625). Gestational age and birth weight did not vary significantly by asphyxial injury (p = NS, p = NS) (Table 2). Although there was no significant difference in 1-minute Apgar scores between the three patterns of asphyxial injury (p = NS), 5-minute and 10-minute Apgar scores did vary significantly between AP, PP, and B types of injury ($p < 0.01$). AP injury and B injuries had lower median 5-minute and 10-minute Apgar scores in comparison to PP injury. First newborn arterial blood gas pH and base deficit also varied significantly based on duration and severity of an asphyxial injury ($p < 0.01$), showing a greater degree of metabolic acidosis in PP and B injuries in comparison to an AP injury. Of the 68 cases with recorded first newborn arterial blood gas pH, 20 (29%) had an AP injury, 19 (28%) had a PP injury, and 29 (43%) had a B types injury. The median arterial pH level was 7.23 (IQR 6.99–7.33) for those with an AP injury, 7.14 (IQR 6.94–7.25) from newborns with a PP injury, and 6.98 (IQR 6.80–7.11) for newborns with B injury. Median newborn arterial base deficit for

Table 1
Common Patterns of Neonatal Hypoxic-Ischemic Injury*†.

Three Common Patterns of HIE	Presentation	Cause	Brain MRI Findings
Acute Profound	Sudden marked decrease in cerebral blood flow and/or oxygenation. Reassuring FHR to category III	Uterine rupture, cord prolapse or acute placental abruption	Abnormal signal in deep gray matter
Partial Prolonged	Reassuring FHR on presentation with intermittent nonreassuring FHR during labor or nonreassuring FHR on presentation with history of decrease fetal movements	Oligohydramnios, cord compression, placental insufficiency, maternal trauma	Abnormal signal in the watershed area of the subcortical white matter and overlying cortical gray matter
Both	Nonreassuring on presentation with terminal near collapse	Pre-existing injury with limited fetal reserves leading to terminal near collapse	Combination of AP and PP

HIE, hypoxic ischemic encephalopathy; MRI, magnetic resonance imaging; FHR, fetal heart rate; AP, acute profound; PP, partial prolonged.
*Patterns of asphyxial injury defined by maternal presentation, fetal heart rate tracing, etiology of HIE, and brain MRI finding.
†Adapted version of table with permission from Muraskas et al.

Table 2
Clinical Characteristics, Blood gases, and Apgar Scores Stratified by Asphyxial Injury.

	Acute Profound		Partial Prolonged		Both		p‡
	n†	Median (IQR)	n†	Median (IQR)	n†	Median (IQR)	
Gestational Age (weeks)	22	38 (37 – 40)	22	39 (39 – 41)	32	39 (38 – 40)	0.35
Birth Weight (grams)	22	3110 (2740 – 3500)	22	3270 (3050 – 3615)	32	3415 (2900–3684)	0.59
First Newborn Arterial Blood Gas pH	20	7.23 (6.99 – 7.33)	19	7.14 (6.94 – 7.25)	29	6.98 (6.80 – 7.11)	< 0.01 *
First Newborn Arterial Blood Gas Base Deficit	20	12 (23 – 10)	18	15 (24 – 13)	26	23 (26 – 20)	< 0.01 *
Apgar (1 min)	21	1 (1– 2)	19	2 (1 – 3)	32	1 (0 – 2)	0.18
Apgar (5 min)	21	3 (1 – 5)	19	5 (3 – 7)	32	2 (0 – 4)	< 0.01 *
Apgar (10 min)	20	4 (2 – 7)	16	7 (5 – 8)	28	3 (1 – 5)	< 0.01 *

n, total number of unique individuals; IQR, interquartile range; p, probability value, pH, potential of hydrogen.
* Denotes statistical significance based on $p \leq 0.05$.
† Total number of cases vary as not all patients had all parameters recorded
‡ Significance in each parameter between three different patterns of asphyxial injury is defined by Kruskal-Wallis. Significant at $p \leq 0.05$

those with B injuries (23 mmol/L, IQR 26–20) and PP injuries (15 mmol/L, IQR 24–13) had a greater base deficit in comparison to those cases of an AP injury (12 mmol/L, IQR 23–10).

A total of 187 newborn creatinine values were observed from 76 cases of HIE (Table 3). Not all cases of HIE had a value for each time frame, although most cases had a newborn creatinine level drawn for at least 2 time frames. For each asphyxial injury type, mean newborn creatinine values peaked during the 13–24 h time frame (Table 3, Fig. 1) and decreased thereafter. Mean newborn creatinine varied significantly by asphyxial injury at the 13–24 h time frame ($p = 0.01$), but not at any other time frames. At 13–24 h, mean newborn creatinine were the lowest at 0.99 mg/dl (95% CI 0.68, 1.30) for those with an AP injury in comparison to 1.35 mg/dl (95% CI 1.02,1.67) and 1.64 mg/dl (95% CI 1.38, 1.91) for those with a PP injury and a B injury, respectively. Mean creatinine values are highest for newborns with B type injuries at 0–12, 13–24, and 25–48 h, although only significantly elevated at 13–24 h of life in comparison to AP and PP.

5. Discussion

In this retrospective study, we compared the rise and normalization of serum creatinine in asphyxiated newborns within the first 96 h of life. Newborns with HIE are at high risk of acute kidney injury (AKI) due to the antenatal asphyxial insult and the ongoing postnatal processes that may ensue such as hypotension, nephrotoxic medication use, and hypoxia [9]. We predicted that newborn creatinine levels could reflect the severity and duration of the perinatal insult categorized by AP, PP, and B injuries. In looking at newborn creatinine trends over time, an AP injury showed minimally elevated creatinine values with rapid normalization. In contrast, PP and B type injuries demonstrated higher creatinine levels in the first 24 h of life with more delayed normalization. These findings may be explained by the acuity and duration of the intrapartum asphyxial event which then triggers the diving reflex. Those newborns with sudden intrapartum asphyxial events such as acute uterine rupture or cord prolapse may not have had sufficient time to centralize blood flow to the more critical organs which resulted in minimal end-organ damage [5]. The PP injury pattern may occur silently in utero during the last weeks of gestation or intermittently in labor that can result in a more sustained diving reflex reducing renal perfusion at the expense of more vital fetal organs. Furthermore in B patterns of injury, a remote insult can deplete fetal reserves and result in terminal collapse (AP) [7, 10]. This concept may also explain our other significant findings in 5- and 10- minute Apgar scores and first newborn arterial blood gases between the different patterns of asphyxia. In PP injuries there are periods of recovery in between intermittent compromise while in AP and B injuries more aggressive resuscitation is required with lower Apgar scores at 5 and 10 min. PP and B injuries have more of a cumulative compromise compared to AP injuries which is reflected in the newborn's first blood gas. Asphyxia normally progresses from a respiratory to a mixed then metabolic acidosis. Although significantly depressed at birth requiring aggressive resuscitation, the AP group studied had significantly better first newborn blood gases compared to the PP and B groups. Although a fetus can tolerate up to 18 min of significant compromise under certain conditions, an AP injury can still result in devastating neurodevelopmental outcomes [11]. The general consensus has been that hospitals should have the capability of starting a cesarean section within 30 min of the decision to operate. Although not a requirement or legal standard, expedited delivery can still result in devastating neonatal outcomes [12].

There are several limitations to this retrospective study. First, it cannot be determined that newborn serum creatinine trends can be a reliable marker with timing of asphyxial injury unless a prospective cohort study has been conducted. Other markers of renal function such as urine output, overall fluid status, blood pressure, glomerular filtration rate, blood urea nitrogen, and serum electrolytes were not evaluated in this study. In addition, newborn serum creatinine levels within the first 12 h of life are thought to be an unreliable marker of newborn renal function as higher newborn values may reflect maternal creatinine and immature renal function [13]. Study patients that did not receive therapeutic hypothermia versus patients that did were not directly compared. Standard of care in the treatment of newborns with suspected HIE has evolved over the years. Approximately 70% of study participants were born after 2010 and received the benefit of therapeutic hypothermia. Therapeutic hypothermia can decrease renal perfusion and

Table 3
Newborn Creatinine Levels (mg/dL) Over Time since Birth, Stratified by Asphyxial Injury.

Time Frame	Acute Profound		Partial Prolonged		Both		p‡
	k†	Mean (95% CI)	k†	Mean (95% CI)	k†	Mean (95% CI)	
0–12 h	7	0.96 (0.50, 1.41)	16	1.18 (0.85, 1.50)	18	1.44 (1.13, 1.75)	0.20
13–24 h	18	0.99 (0.68, 1.30)	16	1.35 (1.02, 1.67)	25	1.64 (1.38, 1.91)	0.01 *
25–48 h	12	0.86 (0.49, 1.22)	15	1.16 (0.82, 1.49)	15	1.45 (1.12, 1.77)	0.06
49–96 h	13	0.69 (0.30, 1.07)	17	1.17 (0.83, 1.51)	15	1.05 (0.73, 1.38)	0.17

k, total number of observations; p, probability value, %, percent; CI, confidence interval.
*Denotes statistical significance based on $p \leq 0.05$.
† Total number of creatinine values vary as not all patients had creatinine drawn within each time frame
‡ Significance in each parameter between three different patterns of asphyxial injury is determined by F tests. Significant at $p \leq 0.05$.

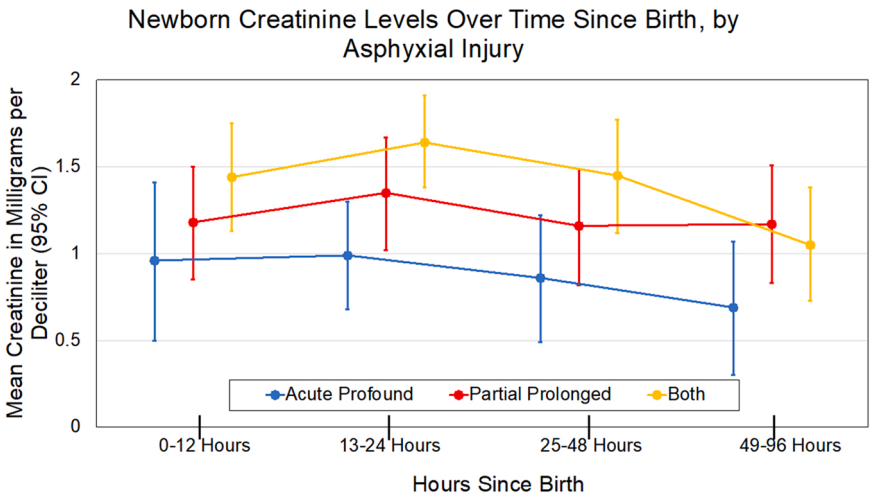

Fig. 1. Newborn Creatinine Levels (Milligrams Per Deciliter) Over Time since Birth, Stratified by Asphyxial Injury. Newborn least square mean creatinine values with corresponding 95% confidence interval (error bars) in the first 0–12, 13–24, 25–48, 49–96 h of life stratified by acute profound (blue), partial prolonged (red), and Both (yellow) type of asphyxial injuries.

GFR. However, randomized controlled trials have demonstrated no significant difference in urine output or creatinine values in cooled versus noncooled newborns [14–16]. Other potential confounders not assessed in this study also include nephrotoxic medication use, the occurrence of hypotension, and the dosing and duration of aminoglycoside antibiotics and vasopressor therapy in our study patients.

Despite total body cooling protocols there is still significant variation on the type and frequency of newborn lab draws in suspected encephalopathy. Our analysis was restricted by the inconsistency of documented information as a result of variable institutional management of neonatal HIE. A retrospective study by Muraskas and Morrison of HIE cases with poor outcomes showed a paucity of objective evidenced-based data that could support or refute an acute intrapartum event sufficient to cause cerebral palsy in term and near-term newborns [17]. This review suggests that newborn creatinine may be another useful and objective marker at discerning timing of asphyxial injury. The rise and normalization of LFTs and NRBCs have also been investigated as potential biomarkers in the timing and duration of perinatal asphyxia. We have previously demonstrated the more chronic the fetal compromise, the more elevated newborn NRBCs and aspartate aminotransferase/alanine aminotransferase (AST/ALT) are shortly after birth with delayed normalization [4,18].

A strength of this retrospective study is the large sample size of a relatively rare occurrence of perinatal asphyxia. This study offers new insight using a common neonatal lab as a potential biomarker for the type of asphyxial insult. It should be noted all cases in this study were reviewed as a result of litigation with adverse outcomes. Although acute intrapartum asphyxia is often a focus of medical litigation, it is only one of the many causes of cerebral palsy. Less than 20% of cases of cerebral palsy can be attributed to an acute intrapartum event [19]. Similar to the placenta, the newborn record can provide valuable information to support or refute allegations of acute intrapartum asphyxia and reduce speculation and non-evidence based expert testimony. By drawing routine newborn labs in a serial manner over the first 96 h of life in a newborn with suspected HIE, the rise and normalization of creatinine can provide objective data to support or refute allegations of acute intrapartum asphyxia.

6. Conclusion

Normal or minimally elevated creatinine levels after birth are consistent with an AP injury. However, if a newborn has creatinine levels elevated shortly after birth with delayed normalization, a remote insult or remote insult leading to limited reserves with an acute component may have occurred. This study recommends that all near term and term newborns with Apgars of 3 or less at 5 min with a cord arterial (venous if arterial is unavailable) base deficit of > -12 have routine newborn labs to monitor multiorgan failure including creatinine on day 1, 2, and 3 of life. We would encourage obstetricians who deliver a depressed newborn with abnormal cord blood gases to request their pediatric colleagues to draw serial newborn creatinine levels and consider NRBCs and LFTs. The placenta can make a great witness and should be sent for examination on all depressed newborns. Although no one test can time injury, a combination of these routine labs with cord gases, newborn blood gases, FHR tracings and newborn imaging can provide valuable information on the duration and timing of a hypoxic ischemic insult.

Conflict of Interest

The authors of this manuscript have no sources of financial support of the study, including provision of supplies or services from a commercial organization. In addition, no funding was received for this work from any organizations. We have no competing interests to disclose.

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Précis

Serum newborn creatinine levels taken within the first 3 days of life can provide evidence-based data on the timing and duration of perinatal asphyxia.

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