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Original Article

Umbilical arterial profiles as predictors of severity of hypoxic ischemic encephalopathy after perinatal asphyxia

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Abstract

Background Perinatal hypoxic-ischemic encephalopathy (HIE) remains a major cause of neurodevelopmental impairment. Umbilical cord blood analysis provides an objective assessment of newborn metabolic status. Accordingly, it is recommended that physicians attempt to obtain venous and arterial samples when there is high risk of neonatal compromise.

Objective To compare the predictive value of umbilical arterial blood pH, lactate and base deficit for subsequent development of severity of hypoxic ischemic encephalopathy (HIE) after perinatal asphyxia and comparison of these parameters to determine which one is superior in predicting severity.

Methods Umbilical cord arterial blood of newborns with perinatal asphyxia was tested for pH, lactate, and base deficit estimation. These newborns were evaluated in level III NICU and divided into two groups. Group 1 had no or signs and symptoms of HIE I and group 2 had signs and symptoms of HIE II/III. Values of pH, lactate, and base deficit were tabulated and analyzed by receiver-operating characteristic curves. Optimal cut-off values were estimated based on the maximal Youden index.

Results Mean pH was significantly lower in group 2 than in group 1, while lactate and base deficit were significantly higher in group 2 than in group 1. Cut-off points for determining severity of HIE were pH <7.13, lactate >6.89 mg/dL, and base deficit >7 mEq/L. Sensitivity and specificity for these cut-off points were 100% and 91.49% for pH, 100% and 85.11% for lactate, and 82.4% and 91.76% for base deficit, respectively. Predictive abilities of all three parameters were similar in determination of HIE severity.

Conclusion Umbilical arterial pH, lactate, and base deficit have excellent accuracy to predict the severity of HIE. All three parameters have similarly good predictive ability. **[Paediatr Indones. 2020;60:24-30; doi: http://dx.doi.org/10.14238/pi60.1.2020.24-30]**.

Keywords: *perinatal asphyxia; pH; lactate; base deficit; HIE; umbilical arterial*

Perinatal asphyxia is an insult to the fetus or newborn due to lack of oxygen and/or perfusion to the brain and other organs. It is often associated with multiple pathophysiologic consequences which lead to multiorgan dysfunction.[1] Perinatal asphyxia can lead to myocardial dysfunction, rhythm abnormalities, acute renal failure, metabolic abnormalities (hypoglycaemia, hyperglycaemia, hypocalcaemia),[2] respiratory failure, necrotising enterocolitis in preterm infants, and coagulation abnormalities. Moreover, hypoxia and decreased perfusion lead to devasting immediate and long term complications of the central nervous system (CNS). Hypoxic-ischemic encephalopathy (HIE) is one such complication, and is among the leading causes of neonatal brain injury, morbidity, and mortality.[3] Severe HIE may have a deleterious impact on newborns, subsequently leading to cerebral palsy, refractory seizures, or strokes.[4] Intrapartum hypoxic events caused an estimated 717,000 deaths in 2010 (1 in 5 of

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all neonatal deaths worldwide).[4] Newborns surviving HIE have a high risk of developing neuropsychological impairment like psychosis, depressive illness, and cognitive impairment.[5]

The relationships between acidosis, base deficit, and lactate to perinatal asphyxia remain inconclusive and data are limited. Some studies have demonstrated a correlation between degree of acidosis, increased lactate, and increased base deficit with the neonatal neurological outcome.[5-7] Other studies suggested that most neurological outcomes are related to disease rather than perinatal asphyxia itself, especially metabolic status like acidosis, increased lactate level, and base deficit.[5,7,8] However, lactate's correlation with perinatal asphyxia has been extensively studied, but the smaller number of studies on acidosis and base deficit relationships to perinatal asphyxia and potential metabolic predictors for HIE severity has left a gap in understanding about birth asphyxia and its impact on neurological outcome.[8]

Depending on severity, neonates with perinatal asphyxia can completely recover, develop permanent disability, or even expire. Thus, caregivers need to know the prognosis in order to make treatment decisions such as neuroprotective strategies like therapeutic hypothermia, or withdrawal of therapy. As such, we aimed to find accurate predictors of HIE severity after perinatal asphyxia.

Methods

This prospective, observational study was carried out in the level III nursery of the *World College of Medical Sciences* (WCMS) Haryana, India, from June 2017 to November 2018. Subjects' parents provided informed consent. The Ethics and Scientific Committee of our hospital approved the study. Intrapartum monitoring of all newborns was done by Doppler ultrasonography and biophysical profile scoring. Sixty-four full term newborns of >37 weeks gestational age in whom asphyxia was suspected were included in the differential diagnosis when there was:[1]

a. Prolonged (>1 hour) antenatal acidosis
b. Fetal HR <60 beats per minute
c. Apgar score ≤3 at ≥10 minutes
d. Need for positive pressure ventilation for >1 minute or first cry delayed >5 minutes
e. Seizures within 12 to 24 hours of birth
f. Burst suppression or suppressed background pattern on EEG or amplitude-integrated electroencephalogram (aEEG).

Neonates with life-threatening congenital malformation, congenital heart diseases, septicaemia, or intracranial bleeding were excluded from this study. Subjects' umbilical arterial specimens were collected and sent to the lab for measurement of pH, lactate, and base deficit levels. Newborns with perinatal asphyxia were evaluated in the level III NICU by department senior residents who were well trained in neonatal neurological examination. Group 1 infants developed either no or signs or symptoms of HIE stage I, and group 2 consisted of neonates who developed symptoms and signs of HIE stage II and III. HIE staging was done by Sarnat classification,[9] as shown in **Table 1**.

Table 1. Sarnat classification of HIE[9]

Variables	Stage I (Mild)	Stage II (Moderate)	Stage III (Severe)
Consciousness	Hyperalert	Lethargic or obtunded	Stupor or coma
Activity	Normal	Decreased	Absent
Neuromuscular control			
a. Muscle tone	Normal	Mild hypotonia	Flaccid
b. Posture	Mild distal flexion	Strong distal Flexion	Intermittent decerebration
c. Stretch reflexes	Overactive	Overactive	Decreased or absent
Primitive reflexes			
a. Sucking	Weak	Weak or absent	Absent
b. Moro	Strong	Weak incomplete/strong	Absent
c. Tonic neck	Slight		Absent
Autonomic function			
a. Pupils	Dilated	Constricted	Variable, unequal
b. Heart rate	Tachycardia	Bradycardia	Variable

Post-natal management of all newborns with asphyxia was done as per protocol. Ventilation was done with CO2 maintained in the normal range; for oxygenation, O2 levels were maintained in the normal range by supplemental O2 and/or mechanical ventilation. For temperature, passive cooling should be done by turning off warming lights to initiate hypothermia as soon as possible after the HI insult. Unfortunately, therapeutic hypothermia could not be given to our subjects because facility is unavailable in our neonatal intensive care setup. Hyperthermia was strictly avoided. Perfusion, cardiovascular stability, and adequate mean arterial blood pressure was maintained to provide adequate cerebral perfusion pressure. Other physiological metabolic states like electrolyte levels, glucose level, and control of seizures, were maintained by appropriate treatment.

All data were collected and analyzed by *SPSS 22* (*SPSS Inc*., Chicago, Illinois, USA) and *MedCalc 18.11* software. The quantitative variables between the two groups were compared using student's T-test (for independent data) and two-tailed Mann-Whitney U test. Results with P values <0.05 were considered to be statistically significant.

The sensitivity, specificity, positive and negative predictive values, and likelihood ratios were computed by receiver-operating characteristic (ROC) curves. The clinical values (cut-off points) were chosen based on the maximal Youden index, corresponding to the combination of highest sensitivity and specificity determined at the apex of the ROC curves.

Results

Our study included 64 neonates who fulfilled the criteria for perinatal asphyxia. Out of these 64 neonates, 15 developed no symptoms of HIE, 32 developed HIE I, 7 developed HIE II, and 8 evolved into HIE III. Two infants who had HIE III clinical features died. Thus, group 1 consisted of 47 (73.44%) neonates and group 2 had 17 (26.56%) neonates. Mean gestational age, gender, mode of delivery, and mean APGAR scores at 5 and 10 minutes were compared between the two groups, but no significant differences were revealed (**Table 2**).

The pH in both groups was acidic, but mean pH in group 2 (6.94) was significantly more acidic than group 1 (7.25). Mean lactate in group 1 (5.74 mg/dL) was significantly lower compared to the results in group 2 (9.94 mg/dL). Comparison of lactate levels of two groups showed statistically significant difference ($P=0.002$). Mean base deficit was 5.4681mEqs/L and 9.82mEqs/L in group 1 & group 2, respectively. Statistical difference of lactate levels among these groups was also significant ($P=0.001$). Lactate and base deficit levels were significantly higher and mean pH was significantly lower in Group 2 compared to those in Group 1, as shown in **Table 2**.

Using the ROC curve analysis of pH, we derived a cut off value of $pH<7.13$, with 100% sensitivity and 91.49% specificity for predicting perinatal asphyxia to evolve into HIE stage II/III. The ROC curve analysis of base deficit revealed a cut-off value

Table 2. Clinical characteristics of patient groups

Parameter	Group 1 (n=47)	Group 2 (n=17)	P value
Total newborns, n	47	17	
Mean gestational age, weeks	38.2	38.5	0.98
Gender, n			
Male	25	9	0.786
Female	22	8	
Mode of delivery			
Vaginal	29	10	0.089
LSCS	18	7	
Mean APGAR score at 5 min & 10min (SD)	5 (2)	4 (1)	0.32
Mean pH (SD)	7.25 (0.09)	6.94 (0.17)	0.0001
Mean lactate level (SD), mg/dL	5.74 (1.66)	9.94 (1.43)	0.002
Mean base deficit (SD), mEq/L	5.4681(1.5)	9.82 (2.12)	0.001

>7, with 82.4% sensitivity and specificity 91.76%, for predicting the development of HIE stage II/III in asphyxiated newborns. The ROC curve analysis of lactate revealed a cut-off point of > 6.89 mmol/L to predict development of HIE stage II/III with 100% sensitivity and 85.11% specificity. The ROC curves are shown in Figure 1 and the analysis results for the 3 variables are shown in **Table 3**.

A comparison of ROC curves for all three parameters revealed no significant differences in predictive ability, as shown in **Table 4** and **Figure 1**.

Discussion

Neuropathological (selective neuronal necrosis, parasagittal cerebral injury, periventricular leukomalacia, focal (and multifocal) ischemic brain necrosis, stroke) and neurological clinical syndromes (cerebral palsy, various seizure disorders,) which are essential components of neonatal neurology are usually the sequelae of HIE. Thus, it is important to be vigilant on biochemical and physiological changes due to hypoxia which are predictive of the structural and functional manifestations of encephalopathy,

Table 3. ROC curve characteristics of variables of umbilical artery blood

Test result variable(s): Umbilical artery	Associated criterion (cut-off value)	Area	Std. error	Asymptomatic sign	95%CI		Sensitivity, %	Specificity, %	Positive LR	Negative LR	PPV, %	NPV, %
					Upper bound	Lower bound						
pH	7.13	0.968	.0202	<0.001	0.891	0.996	100	91.49	11.75	0.00	81	100
Base deficit	>7.00	0.951	0.026	<0.0001	0.866	0.989	82.4	91.76	11.98	0.25	77.8	93.5
Lactate	>6.89	0.952	0.0246	<0.0001	0.867	0.990	100	85.11	6.71	0.00	70.8	100

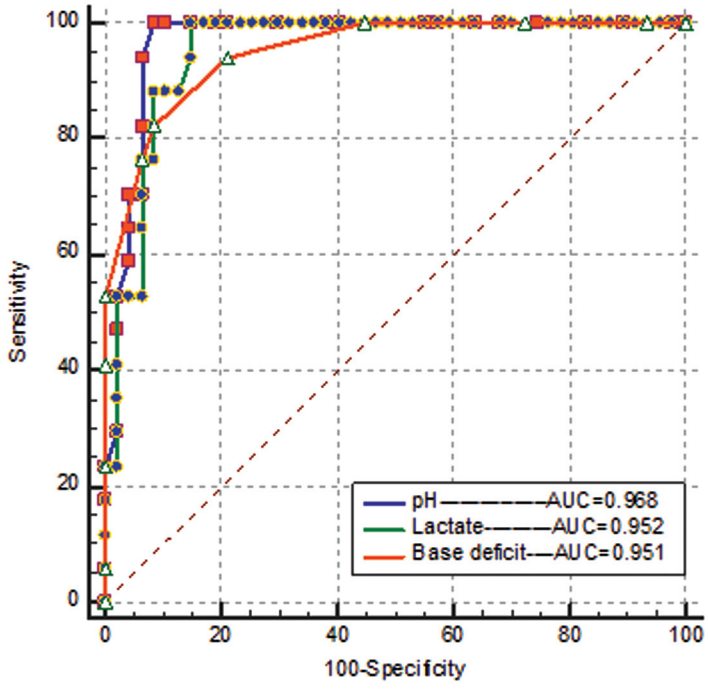

Figure 1. Comparison of ROC curves

Table 4. Pairwise comparison of ROC curves of umbilical arterial blood parameters[10]

Parameters	pH ~ lactate	pH ~ base deficit	Lactate ~ base deficit
Difference between areas	0.0163	0.0169	0.000626
Standard error[10]	0.0289	0.0301	0.0312
95% CI	-0.0404 to 0.0730	-0.0422 to 0.0760	-0.0605 to 0.0617
z statistic	0.563	0.561	0.0201
Significance level	P=0.5737	P=0.5751	0.9840

whether antepartum, intrapartum, or post-partum. To predict the impact of perinatal asphyxia on severity of hypoxic ischemic insult, a variety of criteria have been used, such as APGAR score, which has been used since 1952. The accuracy of these criteria has been questioned because of low sensitivity and specificity. Neonatal acidemia has been associated with increased cerebral blood flow, which can enhance perfusion, thus, preventing hypoxic injury, but later leading to reperfusion injury, which is deleterious to the developing brain.[11] Acidemia due to permissive hypercarbia has been associated with decreased risk for hypoxic injury. However, acidosis due to hyperlactatemia is always associated with increased risk of brain damage.[12]

Our study confirmed a significant association between pH and subsequent development of HIE. Using a cut-off point of pH< 7.13, there was 100% sensitivity and 99.11% specificity for development of HIE stage II/III after perinatal asphyxia. Similar results were reported by a previous study on 250 neonates with acidemia.[13] They found newborn arterial pH of ≤ 7.1 had a strong association with hypoxic-ischemic encephalopathy, neonatal intensive care unit admissions, and a composite adverse outcome parameter. Other studies also reported results similar to our study.[14,15]

Extensive study is available on lactate associations with sequalae of perinatal asphyxia, but few studies could be found on predictive ability of lactate in HIE severity. We found that a lactate cut-off of >6.89 mmol/L had 100% sensitivity and 85.11% specificity for the evolution of perinatal asphyxia to HIE stage II/III. Similarly, a previous study derived a cut-off point of <7.1 mmol/L, with 48% sensitivity and 85% specificity.[16] For measurement of urinary lactate, creatinine ratio >1.0 was found to predict death or impairment, with positive and negative predictive values of 69% and 96%, respectively, in a selected group of neonates with perinatal asphyxia.[17]

Our study showed that base deficit also had a correlation with severity of HIE after birth asphyxia. The cut-off point of >7 mEq/L had 82.4% sensitivity and 91.76% specificity. This finding was in agreement with a study which derived a cut-off point of >7.5 mmol/l, with sensitivity of 94% and specificity of 67%.[16] A previous study found that at base deficit of >11 mmol/L, neonatal complications after perinatal asphyxia increased with 86% sensitivity and 79% specificity.[11] Our lower cut-off point could be because the specimen was from cord blood, while other studies used neonatal arterial blood, either at 1hr after birth or later.[14-16]

Comparing the predictive ability of all three parameters, we found no significant differences, thus, we conclude that all have similarly good predicative ability to determine the subsequent development of severity of HIE after perinatal asphyxia. This finding was in agreement with previous studies.[18-20]

The limitation of our study was the small sample size of study neonates. However, given the catchment area and total deliveries in our hospital and the lower incidence of perinatal asphyxia nowadays because of advanced neonatal science and personnel well-trained in neonatal resuscitation, keeping a confidence interval of 95% and margin of error at 5%, a sample size of 64 is acceptable for any study on perinatal asphyxia.

In conclusion, umbilical arterial blood pH, lactate, and base deficit all have good sensitivity and specificity for predicting severity of HIE in infants with perinatal asphyxia, and are equally effective in such predictions.

Conflict of Interest

None declared.

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