Original Article

Postnatal Lactate as an Early Predictor of Short-Term Outcome after Intrapartum Asphyxia

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OBJECTIVES:

To compare the predictive value of pH, base deficit and lactate for the occurrence of moderate-to-severe hypoxic ischaemic encephalopathy (HIE) and systemic complications of asphyxia in term infants with intrapartum asphyxia.

STUDY DESIGN:

We retrospectively reviewed the records of 61 full-term neonates (≥ 37 weeks gestation) suspected of having suffered from a significant degree of intrapartum asphyxia from a period of January 1997 to December 2001.

The clinical signs of HIE, if any, were categorized using Sarnat and Sarnat classification as mild (stage 1), moderate (stage 2) or severe (stage 3). Base deficit, pH and plasma lactate levels were measured from indwelling arterial catheters within 1 hour after birth and thereafter alongwith every blood gas measurement. The results were correlated with the subsequent presence or absence of moderate-to-severe HIE by computing receiver operating characteristic curves.

RESULTS:

The initial lactate levels were significantly higher ($p = 0.001$) in neonates with moderate-to-severe HIE (mean $\pm$ SD $= 11.09 \pm 4.6$) as compared to those with mild or no HIE (mean $\pm$ SD $= 7.1 \pm 4.7$). Also, the lactate levels took longer to normalize in these babies. A plasma lactate concentration $>7.5 \pm$ mmol/l was associated with moderate-or-severe HIE with a sensitivity of 94% and specificity of 67%. The sensitivity and negative predictive value of lactate was greater than that of the pH or base deficit.

CONCLUSIONS:

The highest recorded lactate level in the first hour of life and serial measurements of lactate are important predictors of moderate-to-severe HIE.

Journal of Perinatology (2004) **24,** 16–20. doi:10.1038/sj.jp.7211023

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INTRODUCTION

Lactate is invariably produced in the event of hypoxia and poor tissue perfusion.[1] When a critical reduction in oxygen and substrate delivery occurs, aerobic metabolism through Kreb's cycle cannot be sustained, and tissues need anaerobic metabolism to meet their energy requirements. This in turn leads to an increase in the production and accumulation of blood lactate.[2] The blood lactate concentrations in critically ill and injured adult patients can be used to detect tissue hypoxia at an early stage, assess illness severity, and predict outcome.[3,4] Recent papers have drawn our attention to the prognostic value of lactacidaemia in newborns with severe hypoxaemia.[2,5]

The relationship between intrapartum asphyxia and neurological abnormalities is controversial. Some studies have demonstrated a correlation between the degree of acidosis and the neonatal neurological outcome.[6] Other studies have shown a poor correlation between metabolic acidosis at birth and neonatal neurological outcome, suggesting that most neurological abnormalities observed during neonatal period are due to causes other than intrapartum asphyxia.[7] When full-term neonates suffer asphyxia during labour or delivery, some may develop HIE with outcomes ranging from complete recovery to death. Caregivers of these sick neonates have been searching for predictors of outcome to facilitate parental counselling, and to provide appropriate levels of care that may include withdrawal of therapy or initiation of neuroprotective strategies. The need for early prediction of outcome is particularly important because of brief therapeutic window and possible side effects of neuroprotective interventions.[8] Based on animal studies and preliminary clinical experience, the therapeutic window in human neonates seems to be within 1 to 6 hours after birth.[9] Thus, it is important to look for useful predictors early in the course of disease, preferably within the first 6 hours after birth. Hence, we undertook this study to determine the role of lactate measurements in the short-term prognosis of asphyxia in term neonates.

The aim of this study was to compare the predictive value of pH, base deficit and lactate for the occurrence of moderate to severe HIE and systemic complications in term infants with suspected intrapartum asphyxia.

MATERIAL AND METHODS

The study was carried out in a level III Neonatal Intensive Care Unit of Nepean hospital which is a tertiary referral centre for high risk neonates in Western Sydney.

Journal of Perinatology 2004; 24:16–20

We retrospectively reviewed the records of all inborn full-term neonates ($\geq$ 37 weeks gestation) suspected of having suffered from a significant degree of intrapartum asphyxia from a period of January 1997 to December 2001. Babies were included in the study group if they satisfied all of the following inclusion criteria:

1. Foetal distress (meconium-stained liquor or abnormal heart patterns such as late or variable decelerations and foetal bradycardia.
2. Depression at birth (Apgar score at 5 minutes less than 5).
3. Haemodynamic, respiratory or neurological abnormalities persisting 30 minutes after birth.
4. Umbilical arterial gas pH <7.0

Neonates with life-threatening congenital malformations, chromosomal abnormalities, intracranial haemorrhage and other causes of impairment than asphyxia, such as septicaemia and pulmonary diseases were excluded from the study.

Clinical signs of HIE, if any, were categorized using the Sarnat and Sarnat classification[10] as mild (stage 1), moderate (stage 2) or severe (stage 3). Stage 1 HIE is characterized by hyperalertness or mild depression of level of consciousness, which may be accompanied by uninhibited Moro and deep tendon reflexes, signs of sympathetic overdrive and a normal or slightly abnormal electroencephalogram (EEG). Stage 2 HIE is characterized by obtundation, hypotonia, diminished spontaneous movements and seizures. Stage 3 HIE is characterized by coma, severe hypotonia, bulbar and autonomic dysfunction and severely abnormal interictal EEG. EEG was not a routine and was performed only in the presence of seizures.

The standard management of HIE consisted of fluid restriction by 30% for the first 48 to 72 hours, maintenance of normal body temperature of $36.5 \pm 0.5^{\circ}C$, ventilation to maintain $PaCO_2$ between 35 and 45 mmHg, maintenance of mean blood pressure above 40 mmHg, anticonvulsants for seizures, normal glucose (2.6 – 8 mmol/l), calcium and magnesium levels. None of the infants were paralysed or sedated. In the presence of neurological symptoms, causes of neurological abnormalities other than asphyxia were ruled out by appropriate investigations.

Base deficit and plasma lactate levels were measured from indwelling arterial catheters within 1 hour after birth before correction of metabolic acidosis with sodium bicarbonate and thereafter along-with every blood gas measurement as per the unit protocol. Blood gases and lactates were analysed immediately after collection using Radiometer ABL 624 analyser (Radiometer A/S, Copenhagen, Denmark).

Patients were categorized into two groups with respect to the neonatal neurological evaluation. Group I included patients with no or mild encephalopathy. Group II included patients with moderate or severe encephalopathy.

The lactate measurements within the first hour were recorded and correlated with the clinical status of the baby. In addition serial measurements of blood lactate were performed and lactate levels at the end of 24 hours were correlated with clinical status of the baby.

Hepatic dysfunction was defined as any of the following: aspartate aminotransferase (AST) >100, alanine aminotransferase (ALT) >100 and prothrombin time>twice normal. Renal dysfunction was defined as haematuria and/or serum creatinine >100 μmol/l (1.5 mg/dl) and urine output <1 ml/kg/hour. Thrombocytopenia was defined as platelet count <10,0000/cmm. Cardiac ischaemia was identified by the need for vasoactive drugs and elevated creatinine phosphokinase; myocardial isoenzyme (CPK MB>25 IU/l).

The chart review was approved by the institutional ethics board and research committee.

Statistical analysis was performed using Statistical package SPSS 7.5 (Statistical Package for Social Sciences, Chicago, IL). The quantitative variables between the two groups were compared using Student's *t*-test (for independent data) and two-tailed Mann–Whitney U test. The comparison of the qualitative variables in the groups was carried out by application of χ^2 test and Fisher's exact test. *p*-Value<0.05 was considered significant.

The sensitivity, specificity, positive and negative predictive values and likelihood ratios were computed by establishing receiver operating characteristic (ROC) curves. The clinical values corresponding to the combination of highest sensitivity and specificity determined at the apex of the ROC curves were chosen.

RESULTS

The annual delivery rate in Nepean Hospital is approximately 6000 deliveries per year and the incidence of HIE is 1 to 2 per 1000 livebirths.

Our study group included 61 term neonates who fulfilled the inclusion criteria. Their clinical evolution was characterized as normal in 35 neonates, mild HIE in seven, moderate in 13 and severe HIE in six. There were three deaths and all of them showed features of severe HIE.

The baseline clinical characteristics of the two groups of patients are summarized in Table 1. The median time of measurement of first level of lactate was 56 minutes (range 49–66 minutes) in group I and 58 minutes (range 48–67 minutes) in group II. The mean lactate levels in the first hour were significantly higher in group II as compared to group I (11.09 ± 4.6 vs 7.1 ± 4.7 mmol/l). Also, we found that the lactate levels normalized slowly in group II as compared with group I. Figure 1 shows the ROC curves for lactate and base deficit in relation to moderate or severe HIE. The clinical value of lactate, base deficit and pH within 1 hour after birth in predicting HIE and systemic complications due to asphyxia is given in Tables 2 and 3. The values correspond to the combination of highest sensitivity and specificity determined at the apex of ROC

Table 1 Clinical Characteristics of Patient Groups

	Group I (n=42)	Group II (n=19)	p-Value
Gestational age (weeks)*	39±1.2	39.2±1.5	0.47
Birth weight (gram)*	3188±733	3225±760	0.86
5 minute Apgar score*	5±2.0	5±2.0	0.53
Delay in respiration* (minutes)	9.8±16.5	17±22.0	0.226
Lactate in first hour* (mmol/l)	7.1±4.7	11.09±4.6	0.001
Base deficit in first hour* (mmol/l)	8.9±5.6	14.3±7.6	0.009
Systemic complications†	13 (31%)	15 (79%)	0.001
Time for lactate to normalize (hour)*	14.2±14	74.6±32.5	0.000

*Mean±S.D.
†No. of patients and percent.

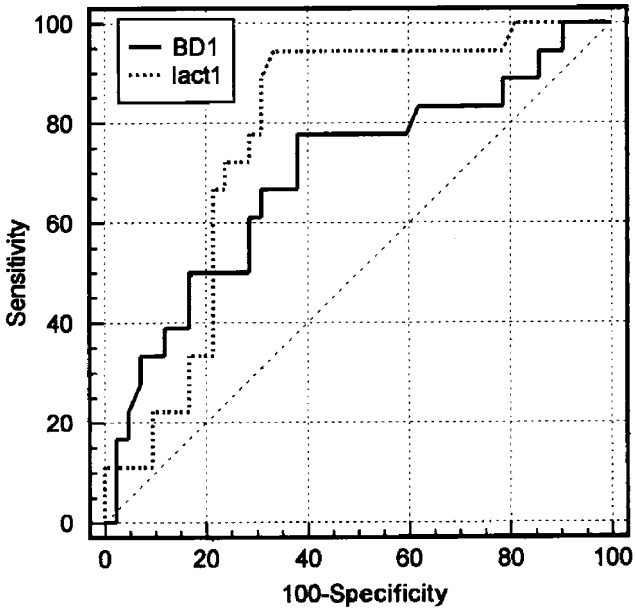

Figure 1. ROC curves for lactate and base deficit at 1 hour in relation to moderate or severe HIE. Area under ROC curve (standard error) was 0.771 (SE 0.071) for lactate and 0.709 (SE 0.076) for base deficit.

curve. Plasma lactate levels lower than 5 mmol/l were not associated with severe encephalopathy while plasma lactate levels >15 mmol/l were associated with moderate to severe HIE in 100% of cases.

DISCUSSION

Hyperlactataemia on admission to the intensive care unit is associated with a high mortality in children.[11] Similar results have been reported in children with septic shock.[12] Neonatal experience is more limited, but hyperlactacidaemia was associated with higher mortality rate in newborns with respiratory distress syndrome,[13] those needing repair for complex congenital heart disease,[14] and in those treated with extracorporeal life support.[15] Cheung et al.[16] predicted that, in neonates with severe hypoxaemia requiring extracorporeal membrane oxygenation, plasma lactate values above 15 mmol/l predicted death. It was also recently recognised that plasma lactate values above 15 mmol/l predict unfavourable developmental outcome in survivors with severe hypoxaemia.[5]

All the above studies have looked at a heterogenous population with multiple aetiological factors. There is a relative paucity of studies evaluating the role of lactate measurements in a homogenous population (neonates with isolated asphyxia, without other diseases affecting their outcome).

We found a strong association between the lactate levels and neonatal neurological evolution. The lactate levels were significantly higher in neonates with moderate-to-severe HIE as compared to those with mild or no HIE. Also, the lactate levels took longer to normalize in these babies.

Neonates are at higher risk of neurological and systemic complications when the blood lactate levels >7.5 mmol/l at 1 hour of age.

Table 2 Clinical Value of Lactate, Base Deficit and pH Measurements ≤1 hour in Evaluation of Neonatal Encephalopathy

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR (+ve test)	LR (−ve test)
Lactate ≤1 hour>7.5 mmol/l	94	67	55	97	2.81	0.08
PH ≤1 hour<7.1	48	85	60	78	3.32	0.61
Base deficit ≤1 hour>−8	79	62	49	87	2.01	0.34

PPV/NPV: positive/negative predictive value; LR (±test): likelihood ratio of positive/negative test.

Table 3 Clinical Value of Lactate, Base Deficit and pH Measurements in Evaluation of Systemic Complications other than HIE

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR (+ve test)	LR (−ve test)
Lactate ≤1 hour 1>7.5 mmol/l	77	70	68	80	2.57	0.32
pH ≤1 hour<7.1	36	85	66	60	2.36	0.76
Base deficit ≤1 hour>−8.0	68	64	62	70	1.87	0.51

PPV/NPV: positive/negative predictive value; LR (±test): likelihood ratio of positive/negative test.

We also showed that a certain level of metabolic acidosis is very often followed by severe neurological symptoms. However, the sensitivity and specificity of base deficit was much lower than lactate levels in the first hour of life. This lack of relation between blood lactate and acid–base parameters may be due to several reasons. Normalization of pH through the administration of alkali is possibly the most important factor. Protons are generated not through the production of lactate but through hydrolysis of ATP and it is possible to have selective increase in anaerobic glycolysis without excess hydrolysis of ATP.[2] There is also some evidence that lactate and hydrogen ions are transported out of muscle at different rates.[2] Thus, lactate ions may be generated without corresponding proton generation leading to poor correlation between base deficit and lactic acidosis.

Similar findings were noted by Silva et al.[1] They measured lactate levels at 30 minutes of life in 115 newborns with suspected asphyxia and found that higher lactate levels were associated with moderate-to-severe encephalopathy.

Frey et al.[17] performed a retrospective analysis on 13 severely asphyxiated neonates and found that neonates who died during first week or had severe brain damage had significantly higher plasma lactate levels than infants with mild or no impairment. Follow-up was for 3 to 19 months and the two groups did not differ in birth weight and pH at the time of lactate determination.

Measurement of urinary lactate: creatinine ratio >1.0 has been 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.[18]

In our study, cord blood lactate levels were not available routinely.

Recently, normal ranges have been established for capillary blood lactate concentrations in term neonates.[19] Furthermore, capillary blood lactate concentrations differ little from arterial concentrations in ill neonates.[19] This would allow capillary blood samples to be used for blood lactate measurements.

Inspite of all the obvious shortcomings of a retrospective review, we did find an increased morbidity with increasing blood lactate levels in a selected homogenous population. In many instances, the blood lactate levels rose before any deterioration in the infant's condition had become clinically apparent.

As neuroprotective therapies such as cerebral hypothermia, free radical scavengers, inhibitors of oxygen free radicals, antagonists of excitatory amnio acids, calcium channel blockers evolve as neuronal rescue strategies, the search for reliable markers becomes more acute.

The predictive value of lactate needs to be validated in a large prospective trial. Blood lactate measurements in conjunction with other parameters may be useful in identifying infants with intrapartum asphyxia who would most likely benefit from intervention.

CONCLUSIONS

Initial highest recorded lactate in the first hour of life and serial measurements of blood lactate are important predictors of moderate-to-severe newborn encephalopathy in cases of intrapartum asphyxia. The sensitivity and negative predictive value of lactate appears greater than either pH or base deficit.

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