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Original Article

Pathology Section

Neonatal Blood Gases and Outcome Following Perinatal Asphyxia

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ABSTRACT

Objective: To determine how well neonatal blood base excess and lactate predict outcome following perinatal asphyxia.

Study Design: Over 68 months, with around 9000 deliveries, lactate was measured on all blood gases taken from neonatal admissions, as well as mineral base and organic acid whenever electrolytes were required. Infants were classified according to their outcome more than 10 years following perinatal asphyxia. Blood gases affected by other causes of acidosis were excluded.

Group I 490 unaffected, including need for resuscitation

Group II 22 unaffected following mild hypoxic ischaemic encephalopathy

Group III 5 unaffected following moderate hypoxic

ischaemic encephalopathy

Group IV 11 disability after acute asphyxia

Group V 8 disability after chronic intrauterine hypoxia

Group VI 5 died from perinatal asphyxia

Logarithmic regression equations of base excess, lactate and organic acid against postnatal age for the first 48 hours were calculated for each group.

Results: Lactate equations increased progressively with the severity of perinatal asphyxia, with similar equations and outcome for groups II and III as well as for groups IV and V. Base excess equations did not increase uniformly and underestimated the severity of asphyxia in group V, because of high mineral base soon after delivery. Organic acid equations ran parallel with lactate but were also increased by low glomerular filtration.

Conclusion: Blood lactate during the first 48 hours predicted the risk following perinatal asphyxia. Lactate above 10 mmol/L at 1 hour indicated risk of adverse outcome, as well as levels above 5 mmol/L after 4 hours, when other causes of acidosis had been excluded. Base excess correlated poorly with lactate because of wide variation in mineral base. It failed to detect chronic in utero hypoxia and was of no value in predicting risk after 8 hours.

Keywords: Perinatal asphyxia, Hypoxic ischaemic encephalopathy, Lactate, Base excess, Mineral base, Organic acid

INTRODUCTION

Base excess measures the metabolic component of acid base balance and is defined as the amount of acid or base needed to restore pH to 7.4 at a normal PCO2 of 40mmHg and temperature 37°C [1]. In Hypoxic Ischaemic Encephalopathy (HIE), it is often taken as a proxy measure of the degree of lactic acidosis, with base deficit >20 mmol/L shown to predict death or disability [2]. In term infants with intra-partum asphyxia, base deficit at 30 minutes was shown to be as good as lactate in assessing the severity of asphyxia [3]. However, base deficit correlates poorly with lactate [3,4], and in preterm and term infants receiving intensive care, adverse outcomes were not predicted by base deficit, but were by lactate levels [4,5]. Studies over the last 40 years have consistently demonstrated the prognostic value of lactate measurements after delivery [3-6]. Moderate or severe HIE is likely to develop at lactate levels above 9 mmol/L at 30 minutes but not at levels below 5mmol/L [3]. Urinary lactate: creatinine ratio over 0.64 in the first 6 hours predicted HIE with 94% sensitivity and 100% specificity, and the degree of elevation predicted adverse outcomes at 1 year [7].

Mineral balance studies show that base excess is determined by both mineral base and organic acid, with organic acid but not mineral base correlating with outcome [8]. This means that only lactate and not base deficit should be used to measure the degree of lactic acidosis. However this recommendation has met with little enthusiasm, partly because of no long term follow up studies.

In order to evaluate a new neonatal Total Parenteral Nutrition (TPN), blood gases obtained from a 5 years cohort of neonatal admissions were prospectively analyzed [9]. Those infants at risk from HIE, very low birth weight or other serious problems have now been followed up for more than 10 years. This study examines the relation between blood gas measurements and outcome following perinatal asphyxia in this cohort of term and preterm infants.

METHODS

Over a 68 months period from 1996 to 2001, lactate was measured on all blood gas samples taken as clinically required from newborn babies admitted after delivery to the neonatal unit in New Plymouth, New Zealand. Whenever electrolyte measurements were also required, Na, K, Ca, Mg, Cl, PO4, protein, urea and creatinine were measured, all on the same blood sample, to allow mineral base and organic acid to be calculated [10]. These protocols were put in place in order to prospectively evaluate a new neonatal TPN regimen [9]. The results were recorded along with antenatal, delivery and postnatal events, clinical and laboratory details and treatments. Data on outcome was obtained by reviewing over 10 years of paediatric follow up of infants who suffered severe perinatal asphyxia or HIE.

Results were expressed as mean ± sample Standard Deviation (SD) and analysis performed with standard parametric tests, linear, logarithmic and power regression analysis.

RESULTS

Over this 68 months period with approximately 9000 deliveries, blood gases were obtained from 582 infants during the first 48 hours, when most episodes of lactic acidosis occurred. How well lactate correlated with base excess and organic acid was determined from arterial blood gases obtained in the first 8 hours from 307 of these infants. This avoided the organic acidosis, with normal lactate, that developed thereafter caused by low glomerular filtration rates [9]. Lactate correlated poorly with base excess because of wide variation in mineral base, as shown in [Table/Fig-1]. High lactate resulted in high mineral base, as shown in [Table/Fig-2]. Sodium bicarbonate and blood products, containing sodium citrate, given after delivery further increased mineral base. Lactate had the expected relationship to organic acid, with correlation coefficients as high as could be anticipated from the error of measuring organic acid [10].

To determine how well lactate and base deficit predict outcome after perinatal asphyxia blood gases from 41 infants presenting with other causes of acidosis were first excluded:

20 with infection

6 with symptomatic congenital heart disease

6 with pulmonary hypoplasia

5 with chromosomal abnormalities or other serious congenital abnormalities

2 with lethal complications from their lung problems

1 with opiod withdrawal

1 who choked while feeding on day 2

Blood gases on standard TPN, which caused high organic acid, were also excluded [9]. The remaining 541 infants were then classified into six groups of increasing severity according to their outcome following perinatalasphyxia. For this analysis the small number of venous and capillary gases were included with the arterial gases because lactate levels are only slightly higher in venous and capillary compared to arterial samples.

Group I unaffected, including infants that needed resuscitation

Group II unaffected following mild HIE

Group III unaffected following moderate HIE

Group IV major disability after acute asphyxia

Group V major disability after chronic intrauterine hypoxia.

Group VI died from perinatalasphyxia.

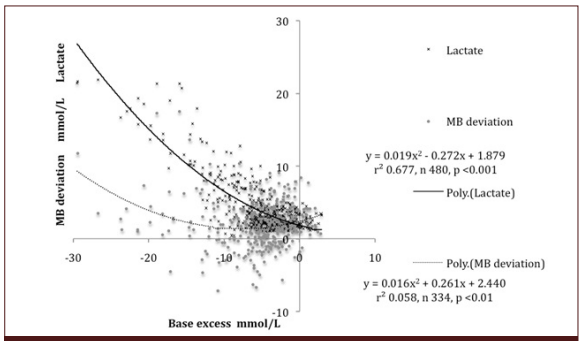
Birth weight and gestational age were similar in the groups, except for group V, most of whom were growth retarded preterm infants, as shown in [Table/Fig-3]. In this cohort, major disabilities attributable to perinatal asphyxia were cerebral palsy and mental retardation. Attention and behavioural problems also affected some children but were not included as major disabilities.

Logarithmic regression equations of base excess, lactate and organic acid against postnatal age in hours (x) over the first 48 hours for each group are given in [Table/Fig-3]. The last figure in each equation provides an estimate at 1 hour after delivery.

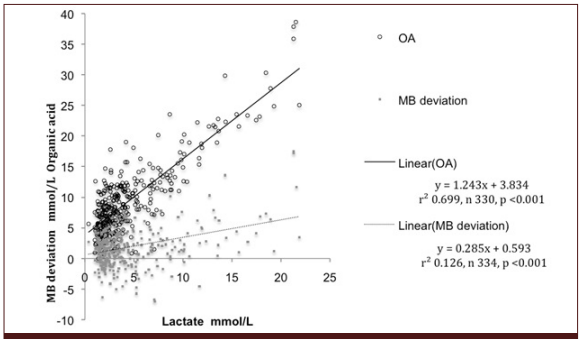
Lactate equations increased progressively with the severity of perinatal asphyxia, with similar equations and outcome for groups II and III as well as for groups IV and V. Base excess equations did not increase uniformly and underestimated the severity of asphyxia in infants with chronic intrauterine hypoxia. These infants, as well as those dying from perinatal asphyxia, had high mineral base soon after delivery, as shown in [Table/Fig-4]. Organic acid equations ran parallel with lactate but were also increased by low glomerular filtration.

Blood lactate during the first 48 hours predicted the risk following perinatal asphyxia, as shown in [Table/Fig-5]. Lactate above 10 mmol/L at 1 hour indicated risk of adverse outcome, as well as levels above 5 mmol/L after 4 hours, when other causes of acidosis had been excluded. There was a high risk of disability and death with lactate above 15 and 20 mmol/L respectively at 1 hour.

Base excess varied widely at any given lactate because of variation in mineral base. It failed to detect chronic in utero hypoxia and was of no value in predicting risk after 8 hours, as shown in [Table/Fig-6]. Both base excess and PCO2 determine pH, which was therefore a poor predictor of outcome, as shown in [Table/Fig-7].



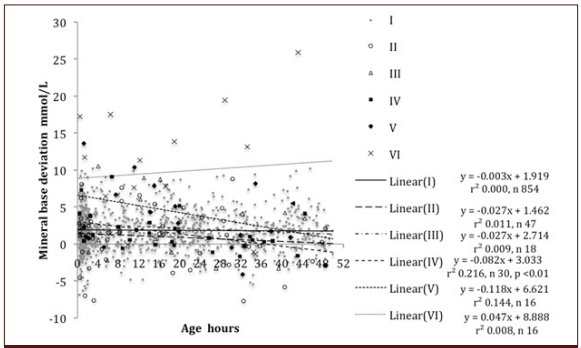
[Table/Fig-1]: Arterial blood base excess predicted lactate poorly in the first 8 hours, because of wide variation in mineral base



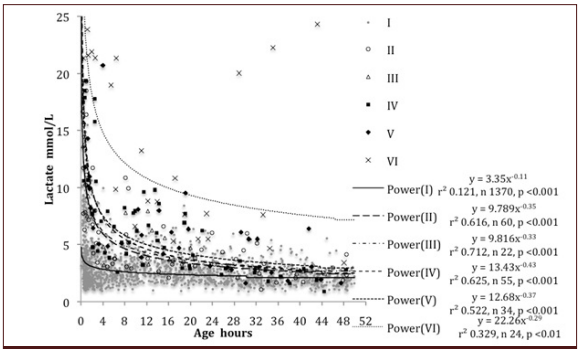
[Table/Fig-2]: Arterial blood lactate increased organic acid as expected in the first 8 hours and also increased mineral base

Group	I	II	III	IV	V	VI
n	490	22	5	11	8	5
Birth weight g	2594 ± 897	3321 ± 781	3818 ± 718	2754 ± 1176	1533 ± 777	3166 ± 847
Gestation week	35.3 ± 3.7	39.4 ± 1.7	40.0 ± 0.7	35.6 ± 4.9	34.1 ± 3.9	38.6 ± 4.3
Base excess	0.44ln(x) – 4.4	2.6ln(x) - 11.0	3.9ln(x) -13.6	4.2ln(x) – 16.1	1.4ln(x) – 8.4	4.1ln(x) – 23.1
mmol/L	r 0.219 n 1259	r 0.686 n 55	r 0.847 n 20	r 0.850 n 55	r 0.381 n 31	r 0.657 n 24
Lactate	-0.49ln(x) + 4.0	-2.3ln(x) + 10.6	-2.1ln(x) + 10.2	-2.9ln(x) + 13.0	-2.3ln(x) + 11.7	-3.4ln(x) + 21.3
mmol/L	r 0.385 n 1370	r 0.762 n 60	r 0.840 n 22	r 0.796 n 55	r 0.688 n 34	r 0.559 n 24
Organic acid	-0.21ln(x) + 8.2	-2.2ln(x) + 14.7	-2.7ln(x) + 16.8	-4.5ln(x) + 21.1	-2.6ln(x) + 18.5	-2.6ln(x) + 32.0
mmol/L	r 0.084 n 854	r 0.539 n 47	r 0.654 n 18	r 0.866 n 30	r 0.480 n 16	r 0.288 n 16

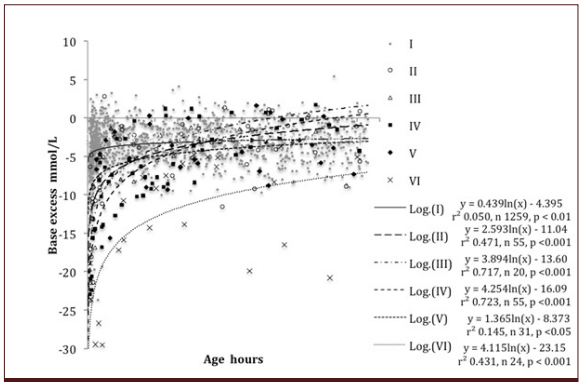
[Table/Fig-3]: Logarithmic regression analysis of blood base excess, lactate and organic acid against postnatal age in hours (x) over first 48 hours. group I unaffected; group II unaffected after mild HIE; group III unaffected after moderate HIE; group IV isability after acute asphyxia; group V disability after chronic hypoxia; group VI died from perinatal asphyxia



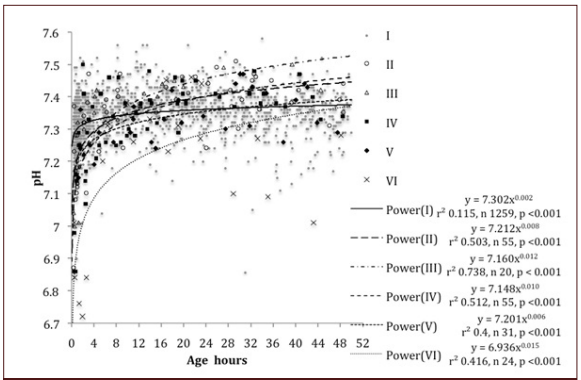
[Table/Fig-4]: Blood mineral base deviation during first 48 hours. group I unaffected; group II unaffected after mild HIE; group III unaffected after moderate HIE; group IV disability after acute asphyxia; group V disability after chronic hypoxia; group VI died from perinatal asphyxia



[Table/Fig-5]: Blood lactate during first 48 hours predicted outcome from asphyxia.
group I unaffected; group II unaffected after mild HIE; group III unaffected after moderate HIE; group IV disability after acute asphyxia; group V disability after chronic hypoxia; group VI died from perinatal asphyxia



[Table/Fig-6]: Blood base excess failed to detect chronic in utero hypoxia and was of no value after 8 hours. group I unaffected; group II unaffected after mild HIE; group III unaffected after moderate HIE; group IV disability after acute asphyxia; group V disability after chronic hypoxia; group VI died from perinatal asphyxia



[Table/Fig-7]: Blood pH was a poor predictor of outcome after asphyxia. group I unaffected; group II unaffected after mild HIE; group III unaffected after moderate HIE; group IV disability after acute asphyxia; group V disability after chronic hypoxia; group VI died from perinatal asphyxia

DISCUSSION

The relation between neonatal blood gas measurements and outcome from perinatal asphyxia was examined in a cohort of newborns delivered before hypothermia treatment became established practice. This confirmed once again the prognostic value of lactate, with levels above 10 mmol/L at 1 hour or above 5 mmol/L after 4 hours, in the absence of other causes of acidosis, indicating increased risk of adverse outcome and need for hypothermia treatment. Lactate was superior to base deficit in predicting outcome particularly in growth retarded babies, who had high mineral base at birth.

The prognostic value of base deficit, shown in [Table/Fig-3], is entirely consistent with a previous study, which found that base deficit and lactate at 30 minutes were equally good at predicting HIE following intra-partum asphyxia in term appropriate or large for gestational age infants [3]. In that study, out of approximately 9200 deliveries, 40 such infants developed HIE [3], compared to our study, where out of about 9000 deliveries, 35 term appropriate or large for gestational age infants developed HIE, but this also affected 16 preterm or small for gestational age infants, who have much higher risks of developing HIE. Their selection excluded infants suffering chronic intrauterine hypoxia [11], as represented by group V infants in our study, who were growth retarded and mainly preterm. These infants developed high mineral base in response to their chronic lactic acidosis [12]. This reduced their base deficits to near normal but failed to lower their lactate or organic acid levels, which were as elevated as those in group IV, suffering an equivalent degree of acute asphyxia.

In that previous study, the correlation coefficient between base deficit and lactate at 30 minutes was reported to be r2 0.51, n 115 (3), lower than r2 0.677, n 480, found in our study in the first 8 hours. However while these values may be highly significant, base deficit varied by as much as 15 mmol/L at any given lactate, as shown in [Table/Fig-1], and cannot be considered a useful proxy measure for either lactate or the degree of organic acidosis. Base deficit does accurately measure the amount of acid or base needed to restore pH to 7.4 at PCO2 of 40mmHg, but this is precisely determined by deviation in both mineral base and organic acid from normal [9].

Our study provides a large number of lactate measurements in infants unaffected by HIE, which should be used as the basis of an expanding collection of lactate measurements in at risk infants with treatment and follow up of their outcome. This would progressively refine the assessment of risk from lactate. This data should also be used as a control to assess the effect of hypothermia on outcome.

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REFERENCES

[1] Siggaard-Andersen O. The acid-base status of the blood. Baltimore: Williams & Wilkins 1964.
[2] Toh VC. Early predictors of adverse outcome in term infants with post- asphyxial hypoxic ischaemic encephalopathy. *Acta Paediatr.* 2000; 89: 343-47.
[3] Da Silva S, Hennebert N, Denis R, Wayenberg JL. Clinical value of a single postnatal lactate measurement after intrapartum asphyxia. *Acta Paediatr.* 2000; 89: 320-23.
[4] Deshpande S, Ward Platt MP. Association between blood lactate and acid-base status and mortality in ventilated babies. *Arch Dis Child.* 1997; 76: F15-F20.
[5] Groenendaal F, Lindemans C, Uiterwaal CSPM, de Vries LS. Early arterial lactate and prediction of outcome in preterm neonates admitted to a neonatal intensive care unit. *Biol Neonate.* 2003; 83: 171-76.
[6] Beca JP, Scopes JW. Serial determinations of blood lactate in respiratory distress syndrome. *Arch Dis Child.* 1972; 47: 550-57.
[7] Huang CC, Wang ST, Chang YC, Lin KP, Wu PL. Measurement of the urinary lactate:creatinine ratio for the early identification of newborn infants at risk for hypoxic-ischaemic encephalopathy. *N Engl J Med.* 1999; 341: 328- 34.
[8] Aiken CGA, Sherwood RA, Kenney IJ, Furnell M, Lenney W. Mineral balance studies in sick preterm intravenously fed infants during the first week after birth. A guide to fluid therapy. *Acta Paediatr Scand.* 1989; Suppl 355.
[9] Aiken CGA. Pathogenesis of metabolic acidosis in preterm infants. *IJNMR.* 2013;1:7-16.
[10] Aiken CGA. History of medical understanding and misunderstanding of acid base balance. *JCDR.* 2013; 7: 2038-41.
[11] Gaffney G, Squier MV, Johnson A, Flavell V, Sellers S. Clinical associations of prenatal ischaemic white matter injury. *Arch Dis Child.* 1994; 70: F101-F06.
[12] Nicolaides KH, Economides DL, Soothill PW. Blood gases, pH and lactate in appropriate and small for gestational age fetuses. *Am J Obstet Gynecol.* 1989; 161: 996-1001.

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