Plasma lactate as a predictor of early childhood neurodevelopmental outcome of neonates with severe hypoxaemia requiring extracorporeal membrane oxygenation

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Abstract

Although plasma lactate concentration has been widely used as an indicator of tissue hypoxia, no clinical study has been conducted to relate these values to the neurological outcome of sick neonates. Seventeen consecutively cared for and surviving neonates with severe hypoxaemia requiring extracorporeal membrane oxygenation (ECMO) were evaluated at a mean age of 19·6 months. The serial plasma lactate concentrations were significantly correlated with the scores of the Bayley Scales of Infant Development. Admission and peak plasma lactate of <15 mmol/l predicted favourable outcome (Mortality and PDI >70 and no disability): sensitivity 100%, specificity 88%, positive predictive value 90%, and negative predictive value 100%.

Plasma lactate values could help predict neurodevelopmental outcome in these sick neonates.

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Severe hypoxaemia in neonates is associated with high mortality and morbidity. Extracorporeal membrane oxygenation (ECMO) has been successfully used as rescue treatment for these newborns with survival rates of about 80% from an international experience of more than 9000 neonatal ECMO cases reported.1 There is limited information available on different risk factors that best predict the outcome of infants receiving ECMO.2–4

Hyperlactataemia is caused by increased production and defective utilisation as both pathways of lactate metabolism are oxygen dependent.5 Therefore, lactate has been used as an indicator of tissue hypoxia. An association with organ damage in hyperlactataemia is supported by animal hypoxic models,6 7 which suggest that plasma lactate values above 15 mmol/l are associated with cerebral damage and concentrations of 25 mmol/l or greater are associated with tissue destruction, cerebral oedema, and death. Despite extensive clinical studies in critically ill adults correlating hyperlactataemia with survival,8 there have been limited clinical studies to address this issue in relation to neurological outcome both in adults and children.

In view of the universal hypoxic ischaemia seen in neonates requiring ECMO, serial plasma lactate values are measured in our unit as part of our routine management of these patients, to indicate tissue hypoxia. We have previously reported very high plasma lactate concentrations in infants requiring ECMO, and their association with high mortality.9 In this study we report the predictive value of plasma lactate and other clinical and biochemical measurements in relation to the neurodevelopmental outcome of infants surviving ECMO.

Methods

From July 1992 to December 1993, 29 infants (birthweights ≥2000 g and gestational ages ≥35 weeks) with severe hypoxaemia requiring ECMO, were consecutively admitted into the neonatal intensive care unit (NICU) at Royal Alexandra Hospital. The ECMO programme at the Royal Alexandra Hospital was the first of its kind in Canada and currently the only one to service the western half of the country. This programme services the four western provinces of Manitoba, Saskatchewan, Alberta, and British Columbia. There are 120 000 deliveries a year in the region. To our knowledge, since the start of the programme, only one infant has been referred for ECMO to the United States because of the unavailability of beds. Twenty-four babies were transferred to the ECMO centre from other level III NICUs, one died before cannulation. To our knowledge, during that period of time, there were no other deaths of infants who were considered candidates and potential referrals to the ECMO programme. Excluding one unrelated surgical death, seven infants (25%) died during the acute illness (six multiple organ failure and one severe intracranial haemorrhage); four (14%) died before 6 months of age (two died after repair of congenital heart disorder, one after withdrawal of treatment because of severe periventricular leucomalacia found two weeks after successful decannulation, one infant with congenital diaphragmatic hernia died four months later secondary to pneumonia). Seventeen children (61%) survived to be assessed at a mean age of 19·6 months; 16 at 17 to 30 months, and one at 10 months of age.

The protocol of management has been outlined before.9 Serial plasma lactate values were studied on admission and every 12 hours thereafter as part of the clinical management for infants referred or considered potential
ECMO candidates. These values were also studied every 12 hours after starting ECMO. Peak lactate concentration was the highest level recorded either before ECMO or within the first 12 hours of initiating ECMO, except for one child with septicaemia who had peak lactate 24 hours after starting ECMO. Our lack of experience in interpreting lactate values in critically ill neonates meant that we did not use the lactate values as criteria for decision making before or during ECMO.

Multidisciplinary assessments of the ECMO survivors at the tertiary NICU neonatal follow up clinics have been described before. Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) were determined by the administration of the Bayley Scales of Infant Development (BSID-II) by reliability tested psychologists or psychometricians. Hearing was assessed by certified clinical audiologists. Apart from knowing that the infants had received ECMO, the assessors were unaware of the clinical state and the laboratory results of the patients. Hospital records and databases of neonatal follow up clinics were reviewed.

In this study, abnormal score in either MDI or PDI was defined as a standard score of >2 SD below the mean of normative data.
correlated \( r=0.79 \), \( P<0.001 \). Regarding the association between primary diagnoses and neurodevelopmental outcome, congenital diaphragmatic hernia was associated with neurodevelopmental disability or abnormal MDI or PDI of borderline significance \( (P=0.05) \). No significant relations were found between neurodevelopmental morbidity and type of ECMO (venoarterial vs venovenous), neonatal seizures, neonatal brain tomography scan results, and respiratory status on follow-up.

No significant correlations were found between the scores of BSID-II and other clinical and biochemical measurements, but the plasma lactate values, on admission, at peak, and 12 hours after starting ECMO were significantly correlated with MDI \( (r=-0.79 \), \( P<0.001 \), \( r=-0.58 \), \( P=0.01 \), \( r=-0.71 \), \( P=0.001 \), respectively); and PDI \( (r=-0.75 \), \( P<0.001 \), \( r=-0.58 \), \( P=0.01 \), \( r=-0.62 \), \( P<0.01 \), respectively) \( (\beta<0.1) \). There were no significant correlations between plasma lactate values and PaO\(_2\), OI, pH and serum bicarbonate concentrations. The serial plasma lactate concentrations of disabled or delayed survivors were also significantly higher than those of normal neurodevelopment (table 2).

Using best subsets regression to analyse the following variables — serial plasma lactate and admission PaO\(_2\) — the values of MDI and PDI could be best predicted with plasma lactate values, on admission and 12 hours after starting ECMO (adjusted \( r^2=0.70 \) and 0.58, respectively). The PaO\(_2\) on admission significantly improved the prediction of MDI but not PDI (adjusted \( r^2=0.78 \) and \( P=0.03 \), adjusted \( r^2 \) to 0.61 and \( P=0.19 \), respectively).

Using an admission plasma lactate value of \( \leq 15 \) mmol/l to predict favourable neurodevelopmental outcome (MDI and PDI \( \geq 70 \) and no disability, prevalence 53\%), the sensitivity and specificity were 100% and 63%, with positive and negative predictive values of 75% and 100%, respectively. The addition of peak plasma lactate \( \leq 15 \) mmol/l improved the specificity to 88% and positive predictive value to 90% (figure). Admission pH \( \geq 7.15 \) predicted favourable outcome with sensitivity 91%, specificity 33%, positive and negative predictive values of 71% and 66%, respectively. Admission serum bicarbonate concentration \( \geq 15 \) mmol/l predicted favourable outcome with sensitivity 91%, specificity 17%, positive and negative predictive values of 67% and 50%, respectively. Both the admission and peak plasma lactate values \( \leq 15 \) mmol/l were associated with favourable neurodevelopmental outcome \( (P<0.005) \). Neither pH nor serum bicarbonate were significantly related to outcome.

**Discussion**

This is the first study on the predictive value and the association of hyperlactataemia with neurodevelopmental morbidity in critically ill infants. There are few clinical data for sick neonates which show an association between hyperlactataemia and mortality, despite extensive studies in critically ill adults. We have previously shown that high lactate values are associated with a high mortality.\(^9\) Using admission and peak plasma lactate values of 15 mmol/l, the outcome of early death and neurodevelopmental disability could be predicted with a sensitivity of 93\%, specificity of 100\%, and positive and negative predictive values of 100% and 90%, respectively.

APACHE II, PRISM II, CRIB and other scoring systems based on a combination of clinical and laboratory measurements have been developed to predict outcome in critically ill adults, children, and newborns respectively.\(^12\)-\(^14\) While no score has been validated for the prediction of long term outcome in sick neonates, plasma lactate values may provide a way of comparing severity of illness and of prognosticating outcome, in addition to the quantification of tissue hypoxia.

This study provides follow up information on the occurrence of neurodevelopmental sequelae in a small group of extremely ill near term newborns. Our study complements the findings of various follow up studies on the neurological outcome of ECMO survivors, showing no association between outcome and demographic data, physiological indicators of severity of illness, or duration of ECMO.\(^2\)-\(^4\)

The association between congenital diaphragmatic hernia and adverse neurodevelopment is consistent with other reports.\(^15\)

Plasma lactate values could be a useful tool in the prognosis of outcome. Other available clinical and biochemical measurements did not seem to be useful. Further prospective studies are required to evaluate the predictive value of hyperlactataemia in these critically ill neonates.

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This follow up protocol had been approved by the Ethics Committee, Glenrose Rehabilitation Hospital.

The information in this paper has been published in part as an abstract (Ped Res 1994; 35: A1300) and presented in part at the Xth Annual CNMC ECMO Symposium, Colorado, 1994.

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**Figure:**

Admission and peak plasma lactate values of 24 neonates requiring ECMO in relation to the outcome (seven early deaths \( \square \), eight with MDI or PDI \( < 70 \) and/or disability \( \bigcirc \), nine normal survivors \( \bullet \)).
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