Intensive Care Med (2000) 26: 314–318

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Early hyperlactataemia in critically ill children

Received: 2 July 1999
Final revision received: 2 July 1999
Accepted: 30 November 1999

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Abstract *Objective*: To examine the relationships between early hyperlactataemia, acidosis, organ failure, and mortality in children admitted to intensive care.
Design: Prospective observational study. Children with lactate levels > 2 mmol/l were eligible for enrolment. Post-operative patients and those with inherited metabolic disease were excluded. Seven hundred and five children admitted to intensive care were screened, and 50 children with hyperlactataemia (incidence 7 %), aged 20.3 months (0.1–191) were enrolled and followed up. The Paediatric Risk of Mortality (PRISM) score, Multiorgan System Failure (MOSF) score, length of ICU stay, and outcome were recorded. Data were collected for lactate (mmol/l), pH, and base excess (BE) until 24 h after admission. Data are reported as median (range) and were analysed by the Mann-Whitney, Fisher's Exact, and Kruskal-Wallis tests, and chi-squared test for trend.
Results: Overall mortality in the screening group was 70/705 (10 %). In the study group (n = 50) median PRISM score was 19 (4–49), median MOSF score 2 (1–4), and observed mortality 32/50 (64 %). Median duration of ICU stay was 6 days (2–32) in survivors, and median time until death 3 days (0–13) in nonsurvivors. Eleven nonsurvivors (34 %) died within 24 h. In the screening group, hyperlactataemia on admission identified mortality with likelihood ratio = 15. In the study group, neither the admission lactate (3.8 vs 4.6 mmol/l, $P = 0.27$), pH (7.32 vs 7.30, $P = 0.6$), nor BE (–7.5 vs –8, $P = 0.45$) differed significantly between survivors and nonsurvivors. Neither the admission nor peak lactate increased with increasing MOSF score ($P = 0.5$ and 0.54). The median peak lactate level was 5 mmol/l (2–9.3) in survivors compared to 6.8 mmol/l (2.3–22) in nonsurvivors ($P = 0.02$), and the cumulative average lactate level was 2.4 mmol/l (1–4.9) in survivors, compared to 4.5 mmol/l (1.6–21) in nonsurvivors ($P = 0.0003$). Persistent hyperlactataemia 24 h after admission identified mortality with likelihood ratio = 7.
Conclusion: Hyperlactataemia on admission to intensive care is associated with a high mortality in children. Nonsurvivors within this group may be distinguished by the peak lactate level, or by persistent hyperlactataemia after 24 h of treatment.

Key words Child · Hyperlactataemia · Lactate · Organ failure · Mortality

Introduction

Lactate, the product of anaerobic metabolism, may reflect the extent of tissue hypoxia in critical illness. Several authors have reported that blood lactate levels predict the development of organ failure or mortality in adults, and some have proposed that lactate may define critical oxygen supply dependency in these patients [1, 2, 3, 4]. However, there are several factors which might confound the interpretation of a lactate level, affecting either the rate of clearance, or augmentation of pyruvate flux, in the absence of tissue hypoxia [5, 6, 7, 9, 10, 11, 12]. Despite the difficulties in interpreting hyperlactataemia, and although the origin of the circulating lactate remains unclear, clinicians treating adults continue to use this parameter as a marker of global tissue dysfunction [7].

We have previously found that lactate levels have only limited prognostic value following cardiac surgery in children [13], whereas others have reported that the lactate level is the earliest predictor of outcome in children with sepsis [14]. We now wished to examine whether the extent and course of early hyperlactataemia (> 2 mmol/l) is related to severity of illness in a heterogeneous group of critically ill children. This study examines the relationship between early hyperlactataemia, conventional acid-base parameters, organ failure, and mortality.

Methods

We designed a prospective observational study set in a 16 bed paediatric intensive care unit (PICU) of a university hospital. Children admitted to the PICU who developed early hyperlactataemia, defined as lactate > 2 mmol/l within 6 h of admission, were eligible for enrolment. Children with an inherited metabolic defect, and those admitted following surgery were excluded.

Seven hundred and five children admitted to the intensive care unit were screened over a period of 18 months. Fifty children with hyperlactataemia (incidence 7 %), median age 20.3 months (range 0.1–191), were enrolled and followed up. Thirty-six patients (72 %) were defined as septic and 14 (28 %) as non-septic [15]. Aetiologic classification of hyperlactataemia is shown in Table 1. The Paediatric Risk of Mortality (PRISM) and Multiorgan System Failure (MOSF) scores, based on the first 24 h (minimum 8 h) of physiological data, were recorded [16,17]. Outcome measures were defined as MOSF score, and intensive care mortality.

Blood was sampled (0.5 ml) for lactate level, pH, and base excess (BE) on admission to the PICU, and repeated at intervals of 2–4 h if clinically indicated. Lactate was measured using the YSI 2300 STAT plus analyser (Yellow Springs Instruments, Ohio, USA). The lactate analyser calibrates at 30 min intervals, for 0 and 5 mmol/l, accepting the calibration if within 2 % of the reference value, and assuming linearity beyond 5 mmol/l. Arterial blood gas samples were measured using the 1640 Electrolyte Blood Gas Analyser (Instrumentation Laboratories, Birchwood, UK). The lactate level, pH, and BE were recorded from the time of admission until 24 h. The cumulative average lactate was calculated for each patient from the sum of all values, divided by the number of values. Since all samples and data were collected for clinical management according to routine practice, clinicians were not blinded to the results, and approval was not sought from the hospital ethics committee.

Data were assumed non-parametric and analysed by the Mann-Whitney, Fisher's Exact, and Kruskal-Wallis tests, and the chi-squared test for trend.

Table 1 Aetiologic classification of hyperlactataemia (> 2 mmol/l) in 50 children admitted to intensive care

Aetiology	n (%)
Non-septic group:	14 (28 %)
Mortality:	10 (71 %)
Tachyarrhythmia	2 (4 %)
Cardiac failure	5 (10 %)
Out of hospital cardiac arrest	4 (8 %)
Seizures	2 (4 %)
Overdose	1 (2 %)
Septic group:	36 (74 %)
Mortality:	22 (61 %)
Staphylococcal septicaemia	2 (4 %)
E. coli septicaemia	2 (4 %)
Group B Streptococcal septicaemia	2 (4 %)
Meningococcal septicaemia	10 (20 %)
Peritonitis	4 (8 %)
Pneumonia	1 (2 %)
Septic shock (no organism isolated)	13 (26 %)
Varicella zoster viraemia	1 (2 %)
Herpes simplex viraemia	1 (2 %)

Results

Organ failure

The median (range) MOSF score in the study group was 2 (1–4), and 2 (1–4) in survivors compared to 3 (1–4) in nonsurvivors ($P = 0.005$). Mortality increased with increasing MOSF score ($P = 0.005$), but there was no significant relationship between either the admission lactate or the peak lactate level, and increasing MOSF score ($P = 0.5$ and $P = 0.54$ respectively) (Table 2).

Mortality

Overall mortality in the screening group was 10 % ($n = 70/705$). Observed mortality in the subgroup of children without hyperlactataemia, who were not enrolled into the study, was 6 % ($n = 38/655$).

In the study group, the median (range) PRISM score was 19 (4–49), and 14 (4–49) in survivors compared to 24 (11–42) in nonsurvivors ($P = 0.003$). Observed mortality was 64 % ($n = 32/50$). The median duration of ICU stay was 6 days (2–32) in survivors, and the median time until death was 3 days (0–13) in nonsurvivors, 11 (34 %) of whom died within 24 h of admission. Using the pre-

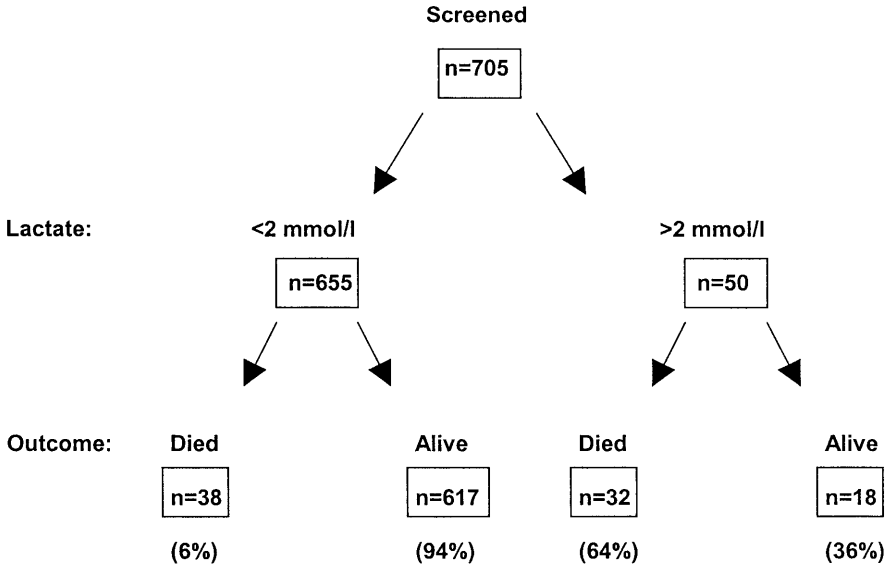

Fig. 1 Mortality in the screened population according to lactate level on admission to intensive care. Pre- and post-test probabilities of death of 10 % and 64 %, respectively. Likelihood ratio = 15 (high diagnostic impact)

Table 2 Mortality, median (range) admission lactate and peak lactate (mmol/l) according to increasing multiorgan system failure (MOSF) score (Chi-squared test for trend)

MOSF score	1	2	3	4	p value
Mortality n (%)	5/14 (36 %)	9/15 (60 %)	8/9 (89 %)	10/12 (83 %)	0.005
Admission lactate	3.9 (0.9–16.6)	4.5 (2.1–16)	5.1 (1.9–16.1)	3.4 (1.2–22)	0.5
Peak lactate	5.3 (2.1–18.7)	5.1 (2.1–16)	6.6 (2.3–20.6)	5.0 (2.4–22)	0.54

Table 3 Median (range) admission lactate, peak lactate (mmol/l), pH, and base excess in survivors (n = 18) and nonsurvivors (n = 32), (Mann-Whitney test)

	Survivors	Nonsurvivors	p value
Admission lactate	3.8 (0.9–8.5)	4.6 (1.2–22)	0.27
Peak lactate	5.0 (2.0–9.3)	6.8 (2.3–22)	0.02
pH	7.32 (6.8–7.6)	7.30 (7.0–7.7)	0.60
Base excess	–7.5 (–14 to 5)	–8.0 (–30 to 3)	0.45

and post-test probabilities of death in the screening population of 10 % and 64 %, respectively, the presence of hyperlactataemia identified mortality with a likelihood ration of 15 (high diagnostic impact) (Fig. 1).

The admission lactate, peak lactate, pH, and BE for survivors and nonsurvivors in the study group are shown in Table 3. Neither the admission lactate, pH, nor the BE differed significantly between survivors and nonsurvivors. However, the median peak lactate level was 5 mmol/l (2–9.3) compared to 6.8 mmol/l (2.3–22) ($P = 0.02$), and the cumulative average lactate level was 2.4 mmol/l (1–4.9) compared to 4.5 mmol/l (1.6–21) ($P = 0.0003$) in survivors and nonsurvivors, respectively. The median time to measurement of the peak lactate was 0 h (0–18) in survivors, compared to 6 h (0–24) in nonsurvivors ($P = 0.08$).

Mortality according to change in lactate is shown in Fig. 2. A persistent hyperlactataemia > 2 mmol/l after 24 h was associated with 93 % mortality ($n = 25/27$), as compared to 30 % ($n = 7/23$) in those children whose lactate level had normalised. Using the pre- and post-test probabilities of death in the study population of 64 % and 93 %, respectively, persistent hyperlactataemia at 24 h identified mortality with a likelihood ratio of 7 (intermediate high diagnostic impact), sensitivity 78 %, and specificity 89 %.

The area under the mortality receiver operating characteristic (ROC) curve for all values of lactate > 2 mmol/l on admission was 0.59 (95 % confidence intervals 0.43–0.76). By contrast, the area under the mortality ROC curve for lactate at 24 h after admission was 0.86 (0.73–0.99).

Aetiology

The median admission lactate was 3.9 mmol/l (1.2–22) in children with sepsis compared to 4.7 mmol/l (0.9–8.3) in children with non-septic illness ($P = 0.57$). There was no significant difference in admission lactate between survivors and nonsurvivors in either the septic ($P = 0.4$), or non-septic subgroup ($P = 0.73$).

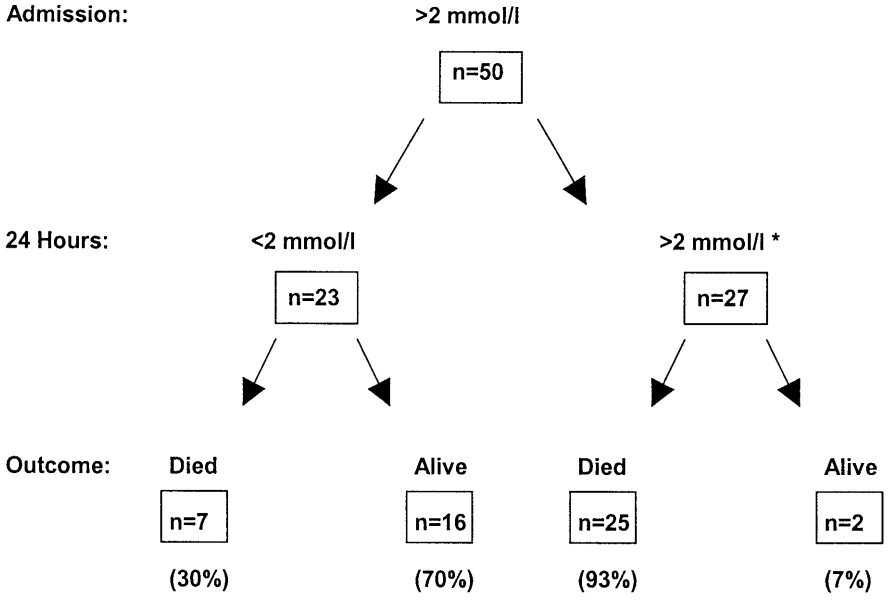

Fig. 2 Mortality according to lactate level 24 h after admission to intensive care. Pre- and post-test probabilities of death of 64% and 93%, respectively. Likelihood ratio = 7 (intermediate high diagnostic impact). * Includes $n = 11$ who died within 24 h with lactate still > 2 mmol/l

Median admission lactate in patients receiving adrenaline by infusion for haemodynamic support ($n = 16$) was 5.7 mmol/l (1.9–22), compared to 3.7 mmol/l (0.9–16) in those who were not receiving adrenaline ($P = 0.06$).

Discussion

The protagonists of lactate measurement in critical illness have suggested that the lactate level may reflect the degree of global tissue anoxia, thus acting as a marker of organ damage and eventual outcome [1, 2, 3, 4, 14]. Others have documented the several factors affecting both clearance and production, which may influence the circulating lactate level [5, 6, 7, 8, 9, 10, 11, 12, 17, 18]. We wished to establish whether the extent of early hyperlactataemia, irrespective of origin, is related to the degree of organ failure and mortality in a heterogeneous group of critically ill children.

Children with hyperlactataemia had both high observed mortality (64%) and severity of illness scores [16, 17]. If the admission lactate level reflects global tissue injury, we might have expected that levels would increase with increasing organ failure scores. Yet although mortality increased with greater organ failure as expected, we demonstrated no such relationship between the lactate level and the MOSF score. Although the presence of hyperlactataemia on admission appears to identify intensive care mortality with a high diagnostic impact (likelihood ratio 15), survivors within this group could not be differentiated from nonsurvivors on the basis of their admission level. These findings suggest that physiological and pathological factors affecting lactate production and clearance in the presence of multiorgan failure may be of sufficient magnitude to confound prognostic interpretation of a single measurement.

It may be more useful to follow the upward or downward trend in lactate, or the duration of hyperlactataemia, by serial measurement after admission to intensive care [1, 3, 4]. In this study, although the extent of admission hyperlactataemia had no additional prognostic value, the peak lactate level, the cumulative average, and the level after 24 h of intensive care differed according to subsequent mortality. This suggests that a failure to respond to early treatment is reflected by a combination of decreased hepatic clearance and increased lactate production irrespective of aetiology. However, the usefulness of this finding in clinical practice is unclear, since nonsurvivors could also be differentiated on the basis of their admission severity of illness (PRISM) score.

We had speculated that the effects of sepsis might increase lactate production even without tissue hypoperfusion, due in part to inhibition of pyruvate dehydrogenase or an increase in pyruvate flux [5, 10, 11, 12, 17]. However, we were unable to demonstrate a difference in admission lactate between septic and non-septic children. The trend for those receiving adrenaline to have higher admission lactate levels was not unexpected, given the tissue hypoperfusion implied by their inotrope requirement. It is unclear how much of this difference in lactate is attributable to tissue hypoxia, or to catecholamine-stimulated glycolysis which exceeds mitochondrial oxidative capacity [17, 18].

In order to assess the significance of hyperlactataemia in these children, we suggest that the lactate level should be interpreted in conjunction with other markers of tissue perfusion and cellular oxygenation, such as the gastric mucosal pCO_2, lactate/pyruvate ratio, or the arterial ketone body ratio [19, 20].

Conclusion

Hyperlactataemia on admission to intensive care is associated with a high mortality in children. Nonsurvivors within this group may be distinguished by the peak lactate, or by the presence of persistent hyperlactataemia after 24 h of treatment.

References

1. Stacpoole PW, Wright EC, Baumgartner TG, Bersin RM, Buchalter S, Curry SH, et al (1994) Natural history and course of acquired lactic acidosis in adults. Am J Med 97: 47–54
2. Friedman G, Berlot G, Kahn RJ, Vincent J-L (1995) Combined measurements of blood lactate concentrations and gastric intramucosal pH in patients with severe sepsis. Crit Care Med 23: 1184–1193
3. Bakker J, Gris P, Coffernils M, Kahn R, Vincent J-L (1996) Serial blood lactate levels can predict the development of multiple organ failure following septic shock. Am J Surg 171: 221–226
4. Deshpande SA, Ward Platt MP (1997) Association between blood lactate and acid-base status and mortality in ventilated babies. Arch Dis Child 76: F15–F20
5. Levraut J, Ciebiera J-P, Chave S, Rabary O, Jambou P, Carles M, et al (1998) Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. Am J Respir Crit Care Med 157: 1021–1026
6. Druml W, Grimm G, Laggner AN, Lenz K, Scheeweiss B (1991) Lactic acid kinetics in respiratory alkalosis. Crit Care Med 19: 1120–1124
7. Kellum JA (1998) Lactate and pHi: our continued search for markers of tissue distress. Crit Care Med 26: 1783–1784
8. Totaro RJ, Raper RF (1997) Epinephrine-induced lactic acidosis following cardiopulmonary bypass. Crit Care Med 25: 1693–1699
9. Levy B, Bollaert PE, Charpentier C, Nace L, Audibert G, Bauer P, et al (1997) Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. Intensive Care Med 23: 282–287
10. Hurtado FJ, Gutierrez AM, Silva N, Fernandez E, Kahn AE, Gutierrez G (1992) Role of tissue hypoxia as the mechanism of lactic acidosis during *E. coli* endotoxemia. J Appl Physiol 72: 1895–1901
11. Hotchkiss RS, Karl IE (1992) Reevaluation of the role of cellular hypoxia and bioenergetic failure in sepsis. JAMA 267: 1503–1510
12. Gutierrez G, Wulf ME (1996) Lactic acidosis in sepsis: a commentary. Intensive Care Med 22: 6–16
13. Hatherill M, Tibby SM, Sajjanhar T, Anderson D, Marsh MJ, Murdoch IA (1997) Serum lactate as a predictor of mortality following paediatric cardiac surgery. Arch Dis Child 77: 235–238
14. Duke TD, Butt W, South M (1997) Predictors of mortality and multiple organ failure in children with sepsis. Intensive Care Med 23: 684–692
15. Saez-Llorens X, McCracken GH (1993) Sepsis syndrome and septic shock in pediatrics: current concepts of terminology, pathophysiology, and management. J Pediatr 123: 497–508
16. Pollack MM, Ruttiman UE, Getson PR (1988) Pediatric risk of mortality (PRISM) score. Crit Care Med 16: 1110–1116
17. Kirschenbaum LA, Astiz ME, Rackow EC (1998) Interpretation of blood lactate concentrations in patients with sepsis. Lancet 352: 921–922
18. James JH, Luchette FA, McCarter FD, Fischer JE (1999) Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. Lancet 354: 505–508
19. Wilkinson JD, Pollack MM, Glass NL, Kanter RK, Katz RW, Steinhart CM (1987) Mortality associated with multiple organ system failure and sepsis in the pediatric intensive care unit. J Pediatr 11: 324–328
20. Gallet D, Goudable J, Vedrinne JM, Viale JP, Annat G (1997) Increased lactate/pyruvate ratio with normal beta-hydroxybutyrate/acetoacetate ratio and lack of oxygen supply dependency in a patient with fatal septic shock. Intensive Care Med 23: 114–116