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Hyperlactetemia and its trends In critically Ill Children Admitted In Pediatric Intensive Care Unit Of A Developing Country

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ORIGINAL ARTICLE

HYPERLACTETEMIA AND ITS TRENDS IN CRITICALLY ILL CHILDREN ADMITTED IN PEDIATRIC INTENSIVE CARE UNIT OF A DEVELOPING COUNTRY

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Background: There is increasing evidence that in setting of critical ailments clinical signs lag biomarkers like Lactate and hyperlactetemia can be the only marker for this disorder. This study was conducted to describe the incidence of hyperlactatemia in critically ill children and its association with outcome. **Methods:** Retrospective review of medical records of all children who had their lactic acid (LA) levels measured during their admission in PICU from January 2014 to December 2015 was done. Demographic and clinical variables were recorded along with PICU therapies, outcome (Survived or expired) and development of multi-organ dysfunction. Results are presented as frequency with percentages and mean with standard deviation. Appropriate statistical tests were applied and *p*-value of <0.05 was taken as significant. **Results:** Total 300 patients had their LA measured and 202 were included in the study. Males were 130 (64%) and mean age was 5.7±4.6 years. Hyperlactatemia was found in 68 (33%) patients and another 75 (37%) had a second LA level >4 mmol/L. Increasing LA trend was found in 79 (39%) patients. Diagnostic categories included cardiovascular diseases (45, 22%), central nervous system diseases (40, 20%), respiratory diseases (31, 15%), sepsis (28, 14%), and gastrointestinal diseases14 (7%). 168 (83%) needed mechanical ventilation. Mean pH was 7.31±0.15 and metabolic acidosis was observed in 91 patients (45%). Mean LA levels in survivors and non survivors were 3.3±3.12 and 5.35±5.47 respectively. Hyperlactatemia was associated with death (*p*=0.01) and development of MODS (*p*=0.03) on univariate analysis. On multivariate logistic regression rising lactate and development of MODS were significantly associated with death (*p*=<0.05, odds ratio (OR) 9.24 (95% confidence interval 1.55–55.20). **Conclusion:** Hyperlactatemia and increasing LA trend in critically ill children are associated with worse outcome in PICU.

Keywords: Hyperlactatemia; outcome, children; trend; PICU
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INTRODUCTION

Critically ill children due to various underlying disease processes often have diminished tissue perfusion. Delay in recognition of hypoperfusion leads to development of multi-organ dysfunction syndrome (MODS). This results in morbidity and increased mortality until it is timely recognized and promptly reversed.[1] There is increasing evidence available that clinical signs lag biomarkers like Lactate and tissue hypoperfusion do not always show clinical signs, hyperlactetemia can be the only marker for this disorder.[1,2] Lactic acid (LA), a by-product of anaerobic metabolism has been used as a biomarker and indicator of tissue hypoxia.[2] This tissue hypoxia may result from respiratory or circulatory disorders.

Hyperlactatemia has been found to be associated with worse outcome in critically ill patients.[3] Its levels and clearance has also been shown to be associated with prognosis in few conditions.[4] While hyperlactetemia has been investigated in some specific clinical scenarios like cardiogenic shock, trauma, sepsis, lactate may also be increased in various other conditions. Only few studies have been conducted in children to evaluate the role of measurement of LA in general population of critically ill children in paediatric intensive care unit (PICU).[5,6]

We report the incidence of hyperlactetemia and its relationship with outcome in critically ill children admitted in PICU of a developing country.

MATERIAL AND METHODS

This study was carried out in PICU of Aga Khan University Hospital (AKUH) which is a 500 bedded tertiary care hospital. PICU at AKUH is four-bedded closed multidisciplinary unit fully equipped with advanced technology with around 450 annual admissions and is staffed by

fellowship trained full-time paediatric intensivists.

Retrospective chart review of all children (aged 1 month to 16 years) admitted in PICU between January 2012 to December 2014 and had a plasma LA measured was done. Study was approved by ethical review committee (ERC) of the AKUH. Patient's medical records were taken from PICU log and rechecked with laboratory data for LA measurement. Patients with a diagnosis of inherited metabolic disorder and patients who remained in PICU for <24 hours were excluded from the study.

Plasma Lactate levels were obtained in potassium oxalate/sodium fluoride vacutainer tubes by a free flow blood samples from arterial or central/peripheral venous lines and were transported to laboratory in ice within 10 minutes. Plasma lactate was measured in laboratory by photometric lactate oxidase enzymatic method on ADVIA 1800 chemistry system, by Siemens. . For quality control three levels of internal quality control materials were used with each batch of analysis. Values of LA were expressed in mmol/L. During the study period College of American Pathologists proficiency testing surveys for lactate were also run and were acceptable.

Patients who had more than one LA levels measured, the first two levels were included for analysis. A trend of these levels were noted and labelled as increasing or decreasing. Hyperlactatemia was defined as LA levels >4 mmol/L based on the data by Bai *et al* who showed an acceptable sensitivity and specificity of LA for prediction of mortality at LA levels >4 mmol/l.[6]

Data was collected on a structured proforma and included demographic details (age, gender), and clinical variables like admitting diagnosis based on dominantly involved system, values of serum creatinine, blood gas analysis, serum electrolytes and serial LA. Data will also be collected on PICU therapies like use of mechanical ventilation, inotrops and development of MODS. MODS was defined as per IPSC 2003 definition.[7] Primary outcome was mortality and development of MODS.

Based on LA levels patients were divided into two groups and labelled as High LA group (LA>4) and Normal LA group (LA <4).

All the data was entered into SPSS v 20. Frequencies with percentages are reported for categorical variables and mean with standard deviation (SD) for continuous variables. Appropriate test (Chi square test and *t*-test) was applied and *p*-value of <0.05 was taken as significant. A logistic regression analysis was performed to determine the factor predicting PICU mortality.

RESULTS

A total 300 patients were identified who had their plasma lactate levels measured out of 933 total admissions and 202 (21.6%) patients were included in the study based on the inclusion and exclusion criteria. Males were 130 (64%) and mean age of the study population was 5.7±4.6 years. Hyperlactetemia was found in 68 (33%) patients who had their LA levels measure and 75 (37%) patients had a second LA level >4 mmol/l. Increasing serum lactate trend was observed in 79 (39%) patients.

Diagnostic categories included cardiovascular diseases (45, 22%), central nervous system diseases including infections (40, 20%), respiratory diseases (31, 15%), sepsis (28, 14%), 14 with gastrointestinal diseases and the rest had other problems (Table-1).

Major individual diagnosis included acute respiratory failure (22), shock (20), status epilepticus (15), and cardiac failure secondary to myocarditis (12), congenital heart disease (10) or cardiomyopathy (5), and acute liver failure (8). Fifteen patients had secondary liver dysfunction as part of MODS. Two patients were admitted with Acute Kidney injury (AKI) and another 40 patients demonstrated AKI as part of MODS. One hundred eighty-eight patients (93%) were admitted from emergency room (ER), nine patients were admitted from operating room (OR) and five patients from ward.

In PICU 168 (83%) patients needed mechanical ventilation, and. MODS was found in 74 (36%) patients while 31 patients (15%) needed cardiopulmonary resuscitation (CPR). twenty-three (11%) patients needed renal replacement therapy (peritoneal dialysis in 10 patients and continuous renal replacement therapy in 13 patients).

Metabolic acidosis was present in 91 patients (45%). Mean pH was 7.31 with a standard deviation (SD) ±0.15 and mean first and second LA levels were 4.08 mmol/l±4.2 and 4.35±4.65 respectively. Mean LA levels in non survivors and survivors were 5.35±5.47 mmol/L and 3.3±3.12 mmol/L respectively.

On univariate analysis hyperlactetemia and increasing LA trend were significantly associated with death (p=0.01) and development of MODS (p=0.032). On multivariate logistic regression analysis increasing LA trend and development of MODS were significantly associated with death. (Table-1).

Table-1: Characteristics of overall study population and difference between survivors and non survivors (n= 202)

Variable		Overall n (percent)	Survivor n (percent)	Non Survivor n (percent)	*p*-value	Odd Ratio (95% Confidence Interval)	Adjusted Odds Ratio
Gender (Male)		130 (64)	77 (38)	53 (26)	0.29	1.37 (0.75–2.51)	
Age (Mean±SD*)		5.78±4.60	5.4±4.47	6.3±4.78	0.20		
Admitting Diagnostic Category	CNS+	40 (20)	28 (14)	12 (6)	0.59		
	CVS-	45 (22)	28 (14)	17 (8)			
	Infections	28 (14)	17 (8)	11 (6)			
	Respiratory	31 (15)	19 (9)	12 (6)			
	Post-Surgical	15 (7)	10 (5)	5 (2)			
	Trauma	12 (6)	7 (3.5)	5 (2.5)			
	GI¨	14 (7)	6 (3)	8 (4)			
Admission Source	ER#	188 (93)	115 (57)	73 (36)	0.60		
	OR^	9 (4.5)	7 (3.5)	2 (1)			
	Ward	5 (2.5)	3 (1.5)	2 (1)			
Mechanical Ventilation		168 (83)	94 (46.5)	74 (36.5)	0.00	0.12 (0.036–0.41)	0.95 (0.244–3.75)
Serum Creatinine (Mean±SD)		0.9±1.03	0.86±1.16	0.99±0.78	0.35		
MODS@		74 (36)	4 (2)	70 (34)	0.00	0.003 (0.001–0.012)	0.002 (0.00–0.13)
Renal Replacement Therapy		23 (11)	9 (4)	14 (7)	0.17	2.86 (1.17–6.98)	6.40 (1.01–40.38)
=ALT (Mean ± SD)		354±984	233±759	539±1236	0.62		
First LA$ Levels (Mean±SD)		4.08±4.26	3.3±3.1	5.3±5.4	0.005		
Second LA levels		4.35±4.65	3.1±3.4	6.3±5.6	0.00		
Hyperlactatemia in First Level		69 (17)	34 (17)	35 (17)	0.008	0.45 (0.25–0.81)	0.29 (0.058–1.46)
Hyperlactatemia in Second Level		75 (37)	32 (16)	43 (21)	0.00	0.27 (0.14–0.49)	1.73 (0.29–10.22)
Increasing LA Trend		79 (39)	34 (17)	45 (22)	0.00	3.74 (2.06–6.86)	9.24 (1.55–55.20)
CPR~		31 (15)	4 (2)	27 (13)	0.00	0.061 (0.020–0.18)	1.29 (0.17–9.71)

*Standard Deviation, +Central Nervous System, - Cardiovascular System, ¨Gastrointestinal System, #Emergency Room, ^Operating Room,@ Multiorgan Dysfucntion Syndrome, = Alanine Transaminase, $Lactic Acid, ~Cardiopulmonary Resuscitation

DISCUSSION

This study provides data on plasma lactate levels in a hetergenous group of critically ill children admitted in PICU of a developing country. Our results show that 7% of patient admitted in PICU had hyperlactatemia and 39% of them had an increasing LA trend. This is similar to that shown by Hatherill *et al* but low as compared to previous data from adults which showed it to be 20–30% in general medical ICU and cardiac surgery.[8–10] These differences could be due to variation in disease states and or time of presentation or time of checking LA levels. Majority of the patients had cardiovascular system disease like myocarditis, cardiomyopathy and different congenital heart diseases followed by central nervous system disease like status epileptics and respiratory diseases like pneumonia. Other diagnosis included infections including septic shock. This shows that patients other than septic shock or heart surgery can also have raised LA level due to similar underlying mechanism of tissue hypoxia.[11,12] Thirty-three patients with first high LA levels developed MODS and 41 patients with MODS had a second high LA. Overall 91 patients had metabolic acidosis on ABGs while LA was elevated only in 68 patients. One Hundred twenty-five patients (62%) from the study population expired. Almost all patients who demonstrated an increasing LA levels expired (77/79). Increased LA trend could be due to continuous LA production because of progressive disease process, tissue hypoxia and organ damage or it could also be due to decreased LA clearance due to renal or liver failure.[13] LA has also been shown to be produced by mechanism other than anaerobic metabolism.[13] Failure to clear LA is considered superior than an isolated single LA value as has been shown by recent studies.[5,14] High LA levels and increasing LA trends were significantly associated with very high mortality in our study. Serial LA monitoring could be more meaningful than a single value as it can provide information on the response to resuscitation and ongoing tissue oxygen deficit and damage to organs.[10,15] This will in turn help in early recognition and prompt reversal as well as titrate the resuscitation efforts and also predict outcome.

Strengths and limitation: To the best of our knowledge this is the first comprehensive report from PICU of Pakistan and the population studied represents a heterogeneous group with various underlying conditions. Our study has the limitations of being a retrospective study with uncontrolled limited data from a single centre. PRISM III score was not calculated.

CONCLUSION

Hyperlactatemia and increasing LA trend in critically ill children are associated with worse outcome in PICU.

AUTHORS' CONTRIBUTION

QA: Conceived the idea, designed the proposal, helped in data collection, analysed data, wrote and edited the manuscript and is the final guarantor of the manuscript. MTJ: Collected and compiled data wrote

and reviewed the manuscript. VK: Collected and compiled data, reviewed the manuscript. LJ: Helped in writing methodology and analysis, reviewed the manuscript. AUH: Conceived the idea, helped in analysis and writing manuscript and reviewed the manuscript.

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