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Association Between Early Lactate Levels and 30-Day Mortality in Clinically Suspected Sepsis in Children

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Abstract
Objective:To determine the correlation between initial levels of lactate and 30-day mortality rate in suspicious cases of sepsis in pediatrics.
Methodology: Study was prospective observational conducted upon 350 patients. The study was held among patients of pediatrics department of Nishtar hospital, Multan. Patients of sepsis were included in the study and were tested for the hypothesis that there is increased risk of mortality with serum lactate levels more than 36mg/dL rather than when levels are less than 36mg/dL. For this, different measurements were taken and compared at different levels of lactate among the patients with sepsis. SPSS version 24 was used to analyzed data and student t-test and chi-square test was applied to see association among variables. P value ≤ 0.05 was taken as significant.
Results: There were 60% (n=105) males and 40% (n=70) females. Comorbidity, oncologic, nononcologic, none and central line present was observed as 74.9% (n=131), 27.4% (n=48), 45.1% (n=79), 32.6% (n=57) and 23.4% (n=41) respectively. Organ dysfunction, hypotension, hematologic, hepatic and renal was noted as 27.4% (n=48), 14.9% (n=26), 17.7% (n=31), 0.6% (n=1) and 16% (n=28) respectively. While, the mean age, heart rate, systolic blood pressure, temperature and pulse oximetry of the 3-day hospital mortality patients was 8.11±4.03 years, 143.21±2.54 bpm, 109.12±3.68 mm Hg, 38.06±1.96 °C and 93.69±2.78 respectively. **Conclusion**: when serum level of lactate is more than 36mg/dL, high risk of mortality is present but with less senistivity. A record of initial levels of lactate may prove to be useful in initial risk detection in sepsis in pediatrics.
Keywords: Lactate, Mortality, Children, Sepsis

Introduction

About more 70000 US Children every year are affected by severe pediatric sepsis. mortality rates ranges between 5-10% inside the hospital [1]. The failure to recognize the sepsis in children at an early stage has led to avoidable mortality [2]. Since the public has shown great concern in the matter of treatable mortality, it has compelled the government to formulate laws for the care of pediatric sepsis and has led to the development of nationwide quality rectification plans for the prevention of sepsis in neonates by the Children's Hospital Association and American Academy of Pediatrics [3]. A great difficulty in this regard is caused by limited diagnostic techniques and trouble in determining the elusive clinical definitions [4].
An effective method for the emergency treatment of adults suffering from sepsis is measuring the venous levels of lactate and it has proved to be "pay-for-performance metric" [5]. Whereas high levels of lactate is a component of adult septic shock definition. there are various factors related to the elevated levels of lactate in sepsis; they include anaerobic glycolysis due to decreased tissue perfusion, bioenergetic feedback to sepsis and diminished clearance which leads to the increased production of lactate [6,7]. When the venous level of lactate is more than 36mg/dL, it increases the risk of mortality in adults, whereas better results have been shown by the application of lactate measurements [8]. Determining the levels of lactated has proved to be propitious with regards to the prognosis and monitoring the benefits of resuscitation [9].
Other than just being a biomarker, the brisk variations in these levels are strongly prognostic during initial treatment of pediatric sepsis. There is reserved documentation regarding the applicability of determination of initial levels of lactate, thence its utility in the guidelines for pediatric sepsis is not approved. This study has been carried out to establish if the early venous levels of lactate in crises of pediatric sepsis is related to the mortality within 30 days interval [10]. An early level of serum lactate more than 36mg/dL is hypothesized in the study to be affiliated with higher mortality rates rather than the concentration at 36mg/dL or less. As a subsidiary investigation, determination of clinical results in the patients organized by levels of lactate was done.

Methodology

The study design was a prospective observational of clinical sepsis formulated to guide the quality of amendment work. It was approved by the related authorities.the study was carried out at emergency department of Nishtar hospital, Multan. The emergency department code consisted of incitement procedure for suspicious cases of sepsis. It included a protocolized assortment of instruments and added members and arranged a set of standard processes to be used rapidly for the induction of IV access, antibiotic administration, fluid resuscitation, along with clinical therapeutics. Testing for lactate is recommended however clinicians have the authority to override the given sequence upon their own judgment.

Study included all the patients registered in the sepsis recognition and treatment registry in the period of initial 45 months of surgery. The exclusion criteria included those patients less than 60 days old or greater than 18 years, transfer of patient separate medical care facility, or those patients whose serum levels of lactate were not measured during initial 8 hours of arrival in ED. Inclusion criteria was based on the assessment of levels of venous lactate. the fundamental end result was mortality rates due to all causes within the hospital stay after 30 days of arrival in ED. The supplementary outcomes comprised of hospital stay more than 3 days, administration of vasoactive agents, ICU stay more than 2 days, days spent on the ventilator, days treated with vasoactive agents.

The primal exposure was an early level of venous lactate more than 36mg/dL. patients having their venous lactate levels calculated within the initial 48 hours were given due consideration. the initially measured levels of lactate were considered only. The levels were determined on the basis of adult data having lactate levels more than 36mg/dL considered a risk factor for mortality. As a supplementary evaluation, levels of lactate were termed as high >36mg/dL, intermediate 18-36mg/dL, and low <18mg/dL and expressed as apt variables. Approved instruments were used to measure the levels of lactate. Medical literature was utilized to determine the covariates, containing variables belonging to risk scoring in pediatric infectious and adult sepsis. In order to determine the aspect of bowel ischemia, operative cases and death were analyzed again to establish if an abdominal origin of sepsis was present, and this abdominal root was taken as the covariate in the analysis of multivariable. In the case of missing lab investigations and values, to determine the organ dysfunction, levels were attributed not beyond the clinical confines as a customary clinical practice. SAS software was used to analyze the data. For the statistics of continuous variables and percentage and frequency of categorical variables, recognized definitive figures were recorded within median range. SPSS version 24 was used to analyzed, mean and SD was calculated for numerical variables like age, systolic blood pressure, heart rate, temperature and pulse oximetery. Qualitative data was analyzed for frequency and percentages like gender and comorbidities. Student t-test and chi-square test was applied to see association among variables. P value ≤ 0.05 was taken as significant.

Results

A total number of 100% (n=350) patients were enrolled in this study, both genders. This study was further divided into two equal groups i.e. 50% (n=175) in each. The mean age, heart rate, systolic blood pressure, temperature and pulse oximetry of the patients lactate level ≤36 mg/dL was 7.28±4.31 years, 142.07±4.09 bpm, 108.20±3.76 mm Hg, 38.99±2.09 °C and 96.08±2.64 respectively. There were 64.6% (n=113) males and 35.4% (n=62) females. Comorbidity, oncologic, Nononcologic, none and central line present was observed as 77.1% (n=135), 36.6% (n=64), 41.7% (n=73), 34.3% (n=60) and 24.6% (n=43) respectively. ED organ dysfunctiona, cardiovascular, hematologic, hepatic and renal was noted as 29.1% (n=51), 24% (n=42), 12.6% (n=22), 9.7% (n=17) and 4.6% (n=8) respectively. While, the mean age, heart rate, systolic blood pressure, temperature and pulse oximetry of the patients lactate level >36 mg/dL was 9.16±5.37 years, 156.04±4.79 bpm, 109.22±4.82 mm Hg, 39.35±2.63 °C and 95.85±2.86 respectively. There were 58.3% (n=102) males and 41.7% (n=73) females. Comorbidity, oncologic, nononcologic, none and central line present was observed as 72% (n=126), 14.3% (n=25), 14.9% (n=26), 54.9% (n=96) and 29.1% (n=51) respectively. ED organ dysfunctiona, cardiovascular, hematologic, hepatic and renal was noted as 26.9% (n=47), 25.1% (n=44), 10.3% (n=18), 15.4% (n=27) and 5.1% (n=9) respectively. The differences were statistically significant of age (p=0.000), heart rate (p=0.000), oncologic (p=0.000), nononcologic (p=0.000) and none (p=0.000). (Table. 1).

The mean age, heart rate, systolic blood pressure, temperature and pulse oximetry of the survived patient was 5.73±4.41 years, 142.62±2.54 bpm, 109.12±3.68 mm Hg, 38.06±1.95 °C and 96.01±1.98 respectively. There were 60% (n=105) males and 40% (n=70) females. Comorbidity, oncologic, nononcologic, none and central line present was observed as 74.9% (n=131), 27.4% (n=48), 45.1% (n=79), 32.6% (n=57) and 23.4% (n=41) respectively. Organ dysfunctiona, hypotension, hematologic, hepatic and renal was noted as 27.4% (n=48), 14.9% (n=26), 17.7% (n=31), 0.6% (n=1) and 16% (n=28) respectively. While, the mean age, heart rate, systolic blood pressure, temperature and pulse oximetry of the 3-day hospital mortality patients was 8.11±4.03 years, 143.21±2.54 bpm, 109.12±3.68 mm Hg, 38.06±1.96 °C and 93.69±2.78 respectively. There were 66.9% (n=117) males and 33.1% (n=58) females. Comorbidity, oncologic, Nononcologic, none and central line present was observed as 94.9% (n=166), 54.3% (n=95), 45.7% (n=80), 2.3% (n=4) and 23.4% (n=41) respectively. Organ dysfunctiona, hypotension, hematologic, hepatic and renal was noted as 46.3% (n=81), 32% (n=56), 39.4% (n=69), 1.1% (n=2) and 9.1% (n=16) respectively. The differences were statistically significant of age (p=0.000), systolic blood pressure (p=0.000), temperature (p=0.001), pulse oximetry (p=0.000), comorbidity (p=0.000), oncologic (p=0.000), none (p=0.000), organ dysfunctiona (p=0.000), hypotension (p=0.000) and hematologic (p=0.000).

Table. 1 Study Population Demographics and Initial Clinical Characteristics by Lactate Level

Characteristics	Lactate Level ≤36 mg/dL (n=175)	Lactate Level >36 mg/dL (n=175)	P Value
Gender			
Male	64.6% (n=113)	58.3% (n=102)	**0.227**
Female	35.4% (n=62)	41.7% (n=73)	
Age (years)	7.28±4.31	9.16±5.37	**0.000**
Heart rate, bpm	142.07±4.09	156.04±4.79	**0.000**
Systolic blood pressure, mm Hg	108.20±3.76	109.22±4.82	**0.028**
Temperature, °C	38.99±2.09	39.35±2.63	**0.158**
Pulse oximetry	96.08±2.64	95.85±2.86	**0.439**
Comorbidity	77.1% (n=135)	72% (n=126)	**0.269**
Oncologic	36.6% (n=64)	14.3% (n=25)	**0.000**
Nononcologic	41.7% (n=73)	14.9% (n=26)	**0.000**
None	34.3% (n=60)	54.9% (n=96)	**0.000**
Central line present	24.6% (n=43)	29.1% (n=51)	**χ^2=0.93,p=0.335**
ED organ dysfunctiona	29.1% (n=51)	26.9% (n=47)	**0.634**
Cardiovascular	24% (n=42)	25.1% (n=44)	**0.804**
Hematologic	12.6% (n=22)	10.3% (n=18)	**0.502**
Hepatic	9.7% (n=17)	15.4% (n=27)	**0.107**
Renal	4.6% (n=8)	5.1% (n=9)	**0.804**

Table. 2 Study Population Demographics and Initial Clinical Characteristics by Mortality Status

Characteristics	Survived	3-day hospital mortality	P Value
Gender			
Male	60% (n=105)	66.9% (n=117)	**0.183**
Female	40% (n=70)	33.1% (n=58)	
Age (years)	5.73±4.41	8.11±4.03	**0.000**
Heart rate, bpm	142.62±2.54	143.21±2.54	**0.048**
Systolic blood pressure, mm Hg	109.12±3.68	109.12±3.68	**0.000**
Temperature, °C	38.06±1.95	38.06±1.96	**0.001**
Pulse oximetry	96.01±1.98	93.69±2.78	**0.000**
Comorbidity	74.9% (n=131)	94.9% (n=166)	**0.000**
Oncologic	27.4% (n=48)	54.3% (n=95)	**0.000**
Nononcologic	45.1% (n=79)	45.7% (n=80)	**0.915**
None	32.6% (n=57)	2.3% (n=4)	**0.000**
Central line present	23.4% (n=41)	23.4% (n=41)	**1.0**
Organ dysfunctiona	27.4% (n=48)	46.3% (n=81)	**0.000**
Hypotension	14.9% (n=26)	32% (n=56)	**0.000**
Hematologic	17.7% (n=31)	39.4% (n=69)	**0.000**
Hepatic	0.6% (n=1)	1.1% (n=2)	**0.562**
Renal	16% (n=28)	9.1% (n=16)	**0.053**

Discussion

Increased levels of lactate are a typical presentation of shock when consumption of oxygen becomes entirely dependant on the delivery of oxygen. In such cases, levels prove to be efficient biological markers and

prognostic tool. As stated by Okorie N et al [11] the levels of lactate represent a measurement of "inadequate perfusion and tissue hypoxia". It has been supported by observation as well as clinical experimentation. it is observed that increased levels of lactate can be regarded as "screening tool" and they assist in the identification of patients having underlying hypoperfusion of tissues before the onset of symptoms.

The normal levels of lactate in the serum are found to be 2mmol/L. hence, Varis E et al [12], found that patients with plasma levels >2mmol/L at the time of admission, suffered high "90-day mortality". While patients having persistently elevated lactate levels, at 72 hours had an even greater 90-day mortality rate. It was observed that time-weighted mean value of lactate at the point of 72 hours and the elevated lactate levels were associated with 90-day mortality independently. Further clinical research is encouraged in this regard to determine the mortality rate in patients with septic shock.

A study performed by --anony [13]showed that there is a correlation between increased levels of lactate/albumin and the progression of MODS as well as mortality in the patients suffering from septic shock and severe sepsis. Lactate/albumin levels were said to be "independent predictor" of MODS in the period of ICU stay. They were predicted to be directly proportional to the "Acute Physiology and Chronic Health Evaluation II score". It shows that if the lactate levels are predetermined, they prove to be useful in predicting the mortality rates in the cases of severe sepsis.

A similar study carried out by Adam J. et al [14] included the patients of same age and gender as well as same levels of lactate and severity of sepsis and SOFA score. At the end of the study, upon administration of POC lactate, it was found that there was remarkable decline the mortality rate and the ICU admissions. It was concluded that introduction of POC lactate levels calculation in emergency department among patients with severe sepsis, not only buys time to test the results and administer IV fluids but also brings about a significant decrease in the rate of mortality and admissions in ICU.

A study conducted by Chertoff J et al [15], demonstrated that in septic patients, the lower levels of plasma clearance were associated with high rates of 30-days mortality and it requires the administration of vasopressors in such patients. The authors refer these levels as useful measurements for directing the treatment in late sepsis. Furthermore, research is advised to determine the underlying process and targets for better clearance of lactate levels in late sepsis to decrease the mortality rates and increase the possibility of better outcomes.

A retrospective cohort study by Filho R et al [16] was showed that increased risk of mortality was associated with early levels of lactate greater than 2.5mmol/L in patients with septic shock or severe sepsis in the emergency department. It should be focused on the importance of decreased levels of lactate as in initiative clue for resuscitation in the severely ill patients for the prevention of morbidity and mortality. Similarly, it was observed by Scott H et al [17], the risk of persisting organ dysfunction decreases with lactate rehabilitation within four hours. The study found out that the relationship between normalization of lactate levels and declining risk of organ dysfunction remains in the groups having initial levels of lactate less than 2mmol/L along with hypotension. The study suggested that a series of measurements of lactate levels in such patients may prove to be a "useful prognostic tool" in the resuscitation during the first few hours of sepsis in pediatrics.

In a systemic review done by Puskarich M [18] it was seen that for the patients admitted in the emergency department, with suspicion of infection, intermediate levels of lactate were correlated with "moderate to high-risk mortality". The authors describe that out of 11062 patients having intermediate levels of lactate during their infection, 1672 patients expired. It was advised for the physicians to closely monitor such patients along with vigorous treatment strategies.

The levels of serum venous lactate are a "promising risk stratification tool" as claimed by Shairo N et al [19]. they found that rate of mortality increases with increase in serum lactate levels. It was based on the observation that out 4.9% of deaths occurred in patients having mildly elevated serum lactate levels, while for moderately elevated levels of lactate, the mortality rate was 9%, similarly patients having severely elevated lactate levels experienced 28.4% mortality. The sensitivity of lactate levels for any death was calculated to be 36 while specificity was found to be 92%. It is suggested that before starting the clinical maneuvers, the comparison of lactate levels must be made.

Another study [20] determines the correlation between early lactate levels and rate of mortality between sepsis in pediatric presented to the emergency department. The study emphasizes the usefulness of testing lactate levels in the emergency rehabilitation of sepsis management in pediatrics. Furthermore, the study confirms the previous researches upon the relationship of initial levels of lactate and organ dysfunction as well as the mortality rates.

Further research is appreciated to determine the better outcome in the management of sepsis by the measurement of lactate levels.

Conclusion

When serum level of lactate is more than 36mg/dL, high risk of mortality is present but with less senistivity. A record of initial levels of lactate may prove to be useful in initial risk detection in sepsis in pediatrics. Further research must be carried out to determine the usefulness of measurment of initial lactate levels in order to have better outcome in pediatric sepsis.

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