ORIGINAL PAPER

THE ROLE OF LACTATE CLEARANCE AS A PREDICTOR OF ORGAN DYSFUNCTION AND MORTALITY IN PATIENTS WITH SEVERE SEPSIS

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ABSTRACT

Background: Little is known about biomarkers which are used to classification of patients in order to diagnosis severity of sepsis among clients of emergency units. It seems that Lactate's clearance can be used in this regard. This study aimed to determine the relationship between Lactate's clearance, mortality and organ's dysfunction with severe sepsis. **Materials and methods:** In this study 90 patients with severe sepsis, were visited and examined exactly. Para clinical tests, serum venous lactate, organ's dysfunction scores, Acute Physiology and Chronic Health Evaluation II (APACHE-II) and Sequential Organ Failure Assessment (SOFA) were applied upon admission and 6 hours after it. According to clinical and laboratory criteria, dysfunction in main organs were examined and Lactate's Clearance was accounted. All the patients were cured according to early goal-directed therapy protocol. **Results:** Among the participants 49 and 41 were male and female respectively. The mean age of the group was 49.37±1.41. The patients were classified to groups, less or more than 10% lactate's clearance. Mortality rate of the patients was 18.9% (17 people). Mean age of the dead group was 49.71±13.33. The mean of dysfunctional organs which is assessed in terms of clinical, laboratory and SOFA criteria was significantly higher among the dead group than other. The Lactate's clearance in the dead group was significantly lower than the other group (p<.05). **Conclusion:** It was concluded that patients with severe sepsis is a marker which is related to tissue hypoxia, also lactate's clearance increasing is related to drastic reduction in biomarkers, mortality, and incidence of organ's dysfunction. Overall, patients with lower lactate's clearance are counted a high risk group for mortality and organs' dysfunction.
Key words: lactate, severe sepsis, prognosis, organ dysfunction.

1. INTRODUCTION

As a part of function promotion programs and based on the published researches, some emergency services and ICUs use lactate serum rate to qualitative resuscitation among patients with severe sepsis, but there is a general concept to use CVP and Scvo2 as physiological purposes of resuscitation. In spite of existing limitations to use CVP as a marker of quantity of intravenous and response to therapeutic liquid, the rate of CVP is relied and repeated measurements of Scvo2 rate is acceptable. If tissue hypo perfusion during the first 6 hours of resuscitation is continued and Scvo2 is less than 70%, inotrope infusion or Packed RBC transfusion can be used to reach hematocrit to 30%. There is a strong recommendation to promote CVP to 8 mm Hg and Scvo2 to 70% during the first 6 hours of resuscitation which is good; however, this is not confirmed as a standard

procedure of the standard care. With respect to prevalence rate in patients with severe sepsis which represent with lactate ≥ 4 mmol/L and hypotension, hypotension solely or lactate ≥ 4 mmol/L solely, were 16.6%, 49.5 and 5.4% respectively, the mortality rate of septic patients with hypotension and lactate ≥ 4 mmol/L is high (around 1.46%) and the index among patients with severe sepsis and lactate (each separately) increase to 7.36% and 4.30% respectively. If Scvo2 is not reachable, normalization of lactate rate can be a practical choice among patients with tissue hypoperfusion due to sepsis. In a cohort study the role of serum lactate level and CRP among patients who were been in hospitals due to sepsis, is examined by Green et al. (2011) and it was finally found out that hyperlactemia is a good index to prediction of mortality rate among the group (1).

Krishna et al. (2009) in a non-intervention prospective

study to determine role of lactate serum level as a predictive factor of shock, showed increasing in lactate levels were very accurate to predict morbidities among patients with sepsis and trauma (2).

Nguyen and colleagues in 2010 did a randomized prospective study and with assessment of lactate serum level and biomarkers (like IL-1, IL-6 receptor antagonist, IL-8, IL-10, TNF-α and so on) upon admission and 6 hours later as well as examination of organs' dysfunction via APACHE2 Showed that fast lactate clearance as an alternative can predict healing of organs' function, good consequence for severe sepsis as well as sepsis shock (3).

In 1999, James and colleagues found out high level of lactate serum among traumatic patients or septic ones is an index of tissue hypoxia and aerobic glycolysis, even when blood pressure, heart output, and urine volume are in an acceptable clinical extension, lactate serum is increased (4).

This study aimed to examine the early and serial serum and lactate clearance level to predict the probability of organs' deficiency among hospitalized patients in emergency units due to severe sepsis or septic shock.

2. MATERIAL AND METHODS

This study is a cross sectional . Among referents to emergency unit of Mashhad's Emam Reza (Iran) from August to December 2012, 90 adult volunteers with the first time sepsis and having research criteria, were studied. Sample size has been counted based on previous study by Jean Bakker et al. in 2006 (5).

Upon admission a complete description of demographic variables, history of medical visits and tests were gathered by researcher, and the tests were repeated 6 hours later. Finally, after definite diagnosis of sepsis, scores for APACHE 2, SOFA, and lactate clearance were recorded from hospitalization to 24 hours after that; the mortality rate was also recorded. The organ dysfunction in 6 main organs, according to table 3 criteria, was checked and the checklists were completed. All patients were informed before including in the study, and they (or relatives) signed a consent which their rights including confidentiality and dignity of the participants during data collection, analysis as well as finding report are cited through. All the treatment steps were done by a therapist; and the second one without any knowledge of treatment, examined the patients' consciousness level and results of tests and exams were recorded. Clinical and physiological laboratory information were collected via APACHE2 system and SOFA's deficiency organ dysfunction upon admission to hospital and 6 hours later. Lactate clearance after serial level of venous lactate is calculated via the following formula

Lactate clearance= {(the early lactate- current lactate) ÷ the early lactate} ×100. The collected data was analyzed by SPSS (19th version).

3. RESULTS

Demographic information

Age: mean age of the male group was 52.16 ± 12.44; the index for females was 46.82 ± 14.09. Chi-square statistics showed no significant difference between the groups. The mean age of the group as a whole was 49.73 ± 1.41

Variables	Frequency	Mean	Min.	Max.	Standard deviation
Age (years)	90	49.73	18	65	13.41
Temperature	90	38.68	35	41	.854
Arterial blood pressure	90	63.67	5.50	110	13.47
Respiration rate	90	28.47	10	44	6.46
Heart rate	90	108.59	54	160	12.63
APACHE2 score	90	20.5	9	30	3.88
SOFA score	90	8.82	4	13	2.01
Lactate serum rate mmol/L	90	2.68	1.5	4.6	.755

Table 1. Physiological, laboratory Assessment of Hospitalized Participants

Variables	Death	Alive
Male	(11) 64.7%	(38) 52.1%
female	(6) 36.3%	(35) 47.9

Table 2. Prediction of mortality rate of genders

Variables	life	Mean	Min.	Max.	SD	Pvalue
Temperature	alive	38.13	36.5	40.5	.9	P=.512
	Passed away	38.09	37.2	39.5	0	
Blood pressure	alive	68.09	7	10	12.8	P<.001
	Passed away	61	50	75	7.3	
Respiration	alive	24.21	12	40	5.5	P=.042
	Passed away	26.11	27	30	2.4	
Heart rate	alive	102.2	72	140	14.7	P=.365
	Passed away	104.11	98	118	5.9	
APAChE2 Score	alive	13.9	5	31	5.2	P<.001
	Passed away	22.64	19	26	3.4	
SOFA Score	alive	5.28	2	12	2.6	P<.001
	Passed away	11.11	9	13	1.6	
Lactate clearance	alive	10.9	0	30	4.9	P<.001
	Passed away	6.88	3	12	3	
Deficit organ	alive	0	0	1	-	P<.001
	Passed away	3	1	4	-	

Table 3. The prognosis of patients 6 hours after study. There is a positive significant relationship between SOFA and APACHE2 (p<.05).

In the Table 1, variable such as age, temperature, and other related variables are presented and indexes like frequency, mean, minimum, maximum and standard deviation are included. Among 90 patients, 17 people passed away (mean age=49.71±13.33), no significant difference between the subgroups' mean and the main groups age. Among the subgroups 64.7% were male and the rest was female, and among alive group 52.1 were male and the rest was female; again no significant difference was seen between the gender groups in terms of mortality rate (p=.597).

Mean of arterial blood pressure at 6 hours of study among the alive group was 68.9±12.98 and for the passed away group 61±7.03 with no significant difference according to Mann-Whitney test (p<.001). Respiration rate of patients per minute at 6 hours of study among alive group was 24.21±5.05 and for the passed away group was 26.11±2.64 which is sig-

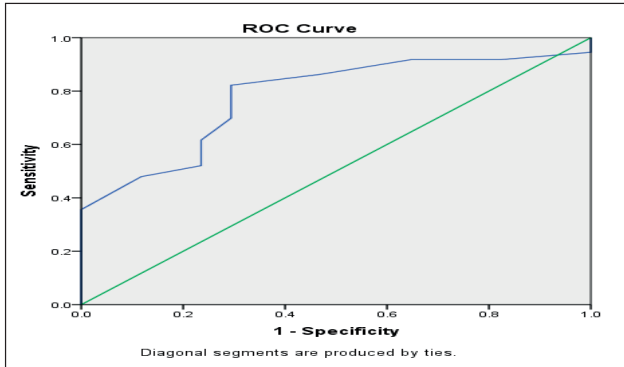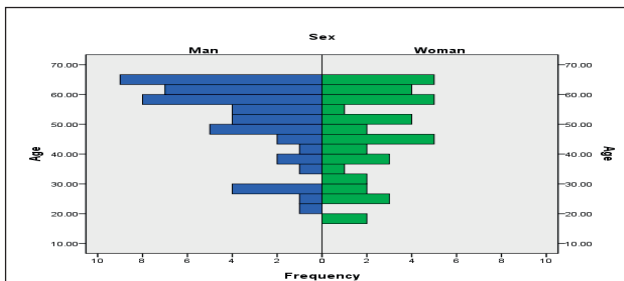| Gender	Lactate clearance		Total
	More than 10%	Less than 10%	
Male	(24) 57.9%	(25) 52.1%	49
Female	(18) 42.1%	(23) 47.9%	41
Total	42	48	90

Table 4. Lactate clearance among patients (gender)

Figure 1. Roc curve of patients' Lactate clearance

Figure 2. Age and organs' deficiency

nificant based on the Mann-Whitney test (p=.042).

Heart rate of the patients per minute among the lively subgroup was 102.2±14.77 and among the other subgroup 104.11±5.99 with no significant difference based on Mann-Whitney test. (p=0365). Score SOFA, 6 hours of study among the alive subgroup was 5.28±2.26, and in the passed away group 11.11±1.36, so the difference was significant in Mann-Whitney test (p<.0001). The rate of lactate clearance at 6 hours of study among the alive subgroup was 10.9±4.99 and for the other subgroup 6.88±3.1, a significant difference in Mann-Whitney test (p<.0001). The mean of deficient organs, 6 hours after study for the alive and passed away groups were 0 and 3 respectively (p<.0001).

Lactate Clearance

In this study, lactate clearance was tested for 2 times (upon admission and 6 hours later); results are included in the Table 4. Patients were classified into 2 groups according to Lactate clearance and previous studies results, (less than 10% and more than 10% Lactate clearance). The index at 6 hours of study for male was 25 (52.1%) and 24 (57.1%) for less and more groups respectively. The situation for female group was 23 (47.9%) and 18 (42.1) respectively as the above mentioned order.

Mortality rate among the groups was 13 (76.5%) and 4 (23.5%) for the less and more groups which is significant in chi-square statistics (p<.05). From total amount, 63 patients showed no deficiency in organs (70%), 12 people (13.3%) one organ, 2 patients (2.2%) 2 organs, 5 people (5.6%) 3 organs and in 8 patients (8.9%) 4 organs or more had deficiency.

4. DISCUSSION

Hemodynamic monitoring is cornerstone for caring of serious patients in emergency units which can be used to diagnosis of Homodynamic instability (6). The index help to change clinical decisions for up to 58% patients, it can also uncover heart-venous situation of patient and lets physician to do a fast intervention (7, 8).

Lactate serum level as an important index in tissue perfusion and oxygenation to tissues is known and it is also counted as an index of metabolic stress. In previous studies, Lactate clearance used as final point in EGDT of severe sepsis, and most of the studies cited clearance rate as 10%.

Findings of this study showed that Lactate clearance can be a sufficient prediction to diagnosis mortality and organs' deficiency after severe sepsis; however, as sepsis threats life, diagnostic biomarkers should have higher sensation; so, the biomarker cannot be used solely.

Berberian and colleagues in 2005 during examination of heart output monitoring of patients found out using common criteria like blood pressure, central venous pressure, and venous oxygen saturation which are weak index of rivavil sufficiency; thus, they strongly insisted using biomarkers such as lactate serum to examine homodynamic.

Jansen et al. (9) examined lactate serum level as predictive of lactate serum level among serious patients and their result was in line with current study. They analyzed lactate serum level of 394 serious patients in ICU upon admission, 12 and 24 hours later and found a significant relationship between the variable and the mortality rate; however, no relationship was found between the variables among non-septic patients. They concluded that there is an obvious relationship between lactate serum level and the patients' prognosis during the first 24 hours of hospitalization which is in line with the current study.

In many studies, naturalized lactate level among patients with severe sepsis was associated with improvement of the patients. Abramson et al. (10) found that reduction in lactate to less than 2mmol/L during the first 24 hours of treatment was combined with the patients healing.

The current study showed a positive significant relationship between APACHE2 score and SOFA with mortality rate of hospitalized patients. It was also observed that the means scores of APACHE2 and SOFA upon the hospitalization were 20.5 and 88.2 respectively, and after 6 hours hospitalization in emergency unit APACHE2 score were 13 and 22 for lively and passed away groups respectively. The 6 hours SOFA scores were 5 and 11 for the groups as the above mentioned order. Similar studies (11-13) in Iran are in line with the results, so it is suggested that with increasing in APACHE2 score, more caring is necessary.

In our study, significant relationship was found between number of deficient organs and mortality rate and increasing in APACHE2 score. The situation can be ascribed to severity of diseases as well as insufficient early treatments or delayed resuscitation activities.

In some studies, mortality rate of severe septic patients among 41% early lactate level and more than 3.5mmol/L was reported.

Rivers et al. (14) used early goal-directed therapeutic protocol during the first 6 hours which led to tissue hypoxia

reduction, 16% reduction in mortality rate of severe septic group and in effect reduction in lactate level.

There was also an improvement in tissue hypoxia after a short term prescription of vasopressors; however, long term taken of the medicine can lead to reduction in lactate clearance as well as improvement (15). In a randomized study, it was also found that the early intervention led to 16% reduction in mortality rate. In several studies it was reported that having fluids, vasopressors and blood in experimental groups with increasing lactate to 20% during 2 hours, led to drastic reduction among hospitalized group with severe sepsis.

We did not examine infectious origin of patients. According to Kobayashi et al. (16) hematologic disorders (like leukocytosis, anemia, and thrombocytosis) are common among severe septic group. Change in coagulation mediators and fibrinolysis is associated with DIC and increasing in mortality rate. Patients with severe sepsis who suffer from DIC show serial lactate serum level. Mortality rate increases with number of deficient organs, so that one organ's deficiency is associated with zero mortality, 2 the organs (15.99% mortality), 3 the organs (22.4% mortality) and 4 organs (28.6% mortality) which are in line with the previous studies.

In previous studies lactate level per se was used to predict situation of hospitalized patients in ICUs. Lee TR et al. study (17) a significant relationship was found between neurological consequences among patients with lactate clearance during 6 hours of beginning treatment.

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