Lactate Clearance is a Prognostic Factor in Patients on Shock State

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ABSTRACT

Aim is to determine whether lactate clearance has value as mortality prognostic factor in shock patients, or not. A scrutiny, descriptive, prolective, homodemic, longitudinal study in patients older than 19 years, excluding chronic renal illness, hepatic insufficiency, neoplasias and diabetics on biguanides treatment, was performed. Arterial gasometry was used to obtain lactate rates at admission, 6, 12, and 24 hours as well as lactate's clearance. Determinations between survivors and not survivors were compared, as well as correlation with APACHE II was performed. 41 patients were studied, 53.7% women and 46.3% men, mean age was 63.95 years. The diagnostics were septic shock in 29.2%, hypovolemic 63.4%, and cardiogenic 7.3%. The mortality in cardiogenic shock was 100%, with null lactate clearance. The survival rate was higher in hypovolemic shock as its lactate clearance rates (at 12 and 24 hours). Lactate clearance rates of less than 0 at 24 hours had a positive predictive value and a sensitivity of 80%. Lactate clearance at 6, 12, 24 hours among survivors and not survivors demonstrated statistical significance in the Univariate Analysis (p<0.002, p<0.000, p<0.000) respectively. The lactate clearance rate at 24 hours is a prognostic factor for mortality in patients in shock state.

Key words: *Lactate clearance, prognostic factor, shock state.*

Laktat Klirensi Şok Durumundaki Hastalarda bir Prognostik Faktördür

ÖZET

Çalışmanın amacı laktat klirensinin şok durumundaki hastalarda mortalite prognostik faktörü olarak bir değerinin olup olmadığını değerlendirmektir. Bu çalışma 19 yaşından büyük hastalarda kronik hastalıklar, hepatik yetmezlik, kanserler ve biguanid tedavisi kullanan diyabetik hastalar dışlanarak yapılan açıklayıcı ileriye dönük, homodemik bir çalışma olarak yapıldı. Laktat klirensi ve aynı zamanda başvuruda, 6, 12 ve 24. saatlerde laktat oranlarını ölçmek için arteryal gazometre kullanıldı. Hayatta kalan ve ölenlerin bulguları ve APACHE II'leri arasındaki korelasyon karşılaştırıldı. Kırk bir hasta çalışmaya alındı. %53.7'si kadın, %46.3'ü erkekti, yaş ortalaması 69.95 yıl idi. Tanılar %29.2 hastada septik şok, %63.4 hastada hipovolemik ve %7.3 hastada kardiyojenik şoktu.Kardiyojenik şokta mortalite sıfır laktak klirensle birlikte %100 idi. Laktat klirensi gibi survival oranları hipovolemik şokta daha yüksek idi (12 ve 24. saatlerde). 24 saatte o'dan küçük laktat klirens oranları pozitif prediktif değere ve %80 sensitiviteye sahipti. Univariate analizde, 6, 12 ve 24. saatlerde yaşayanlarda ölenler arasında laktat klirensinde istatistiksel anlamlılık tespit edildi (sırasıyla, p<0.002, p<0.000, p<0.000). 24. Saatteki laktat klirens oranı şok durumundaki hastalarda mortalite için bir prognostik faktördür.

Key words: *Laktak klirensi, prognostik faktör, şok durumu*

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INTRODUCTION

Shock state is one of the most frequent emergencies in our hospital and all over the world. The cause is variable; in many cases if detected early it is possible to avoid vital organs to be damaged. It represents unbalance in offer and demand of oxygen, as the organs are in hypoperfusion the lactate production raises, for that, its clearance represents a prognostic factor (1-3). The term shock has become synonym of hypotension (2), but in a complete definition it is an imbalance on offer of oxygen, nutrients and tissue demands, in occasions because of raised tissue metabolism. Severe hypotension is considered a decrementing value in systolic pressure of more than 40 mmHg in a normal pressure (90 mmHg) in hypertension patients as well as a median arterial pressure of less than 65mmHg in adults along with oliguria, neurologic alterations, low capillary refill, tachypnea, and tachycardia (1-5). For each organ failing, the mortality raises 15%. Patient's mortality in shock state ranges from 20 to 54% (4).

When shock becomes, adenosintriphosphate (ATP) increase is necessary to maintain vital functions, however, in oxygen absence it is produced by the anaerobic glucolysis mechanism. The response is to accumulate energy for vital organs function, for that, perfusion to some organs decreased. Arterial receptors detect decrease on pressure activating a hormonal response through the hypothalamic – pituitary axis stimulating the sympatic via resulting on increase production of circulating norepinephrine, adrenaline, glucagon, cortisol and rennin. The cardiac output, peripheral resistance, glucolysis, and gluconeogenesis raises. At the same time waste products accumulate from tissue metabolism and inflammatory mediators are produced, producing academia that perpetuates the failure (5-7).

It is well known that hyperlactacidemia is correlated with mortality in critically ill patients. Lactate production is not only originated by anaerobic metabolism, but by mediators of inflammatory response, catecholamine's, endotoxins 2,3 and decreased of lactate clearance by the liver (8-10). Elevated seric lactate concentrations are found in hepatic cirrhosis, renal failure, diabetes mellitus, cancer, convulsions, cholera, acute pancreatitis and use of pharmaceutics (biguanides, isoniazide, nitroprusiate, ethanol, salicylates, lactulose, etc.) for that, these conditions may alter prognostic value interpretation of the hyperlactacidemia in shock patients (6,9,10). We consider that lactate clearance determination may be a better prognostic factor of organic failure and mortality, because patients with high lactate clearance have less mortality rate than those with low lactate clearance. The best lactate clearance rate is correlated as well with decreased in some biomarker such as interleukins 1,6,8,10, tumor necrosis factor alpha, caspase 3. On the other hand, some studies have demonstrated that normal lactate rates can be found on cardiogenic shock, acute renal failure, and that lactate clearance are altered on these, probably because of multiorgan failure (9,10-16). On the majority of studies performed, the effectiveness of lactate clearance determination are compared to predictors mortality scores such as APACHE II, SOFA, SAPS II, concluding that lactate clearance may be by itself a good mortality prognostic factor (12-16).

The objective of this paper is to determine the Lactate Clearance Mortality Prognostic Factor in Shock Patients.

MATERIALS AND METHODS

A Scrutiny, descriptive, prolective, homodemic, and longitudinal study was performed. Patients on shock state received at the emergency room of the Hospital General Regional No. 36 from Instituto Mexicano del Seguro Social, in Puebla, México, with lactate clearance were included. We excluded patients with chronic renal failure, hepatic insufficiency, neoplasias and diabetic patients on biguanides treatment. Variables included in the study were, age, gender, mortality, type of shock, lactate levels, APACHE classification, PCO_2, and lactate clearance. Univariate analysis of these variables was performed. We measure the arterial lactate clearance by using GEM Premier 3000 (Instrumentation Laboratory) at 6, 12 and 24 hours after admission of the patients and compare the results between survivors and not survivors on different states of shock. For the continue variables the t-student test was used, attending the number of patients evaluated, as well as data behavior (normal distribution). On the categorical variables the Mann-Whitney U test was used. Multivariate analysis was performed and for the variables resulting with statistical significance logistical regression was made. In addition, a ROC curve was made to determine the lactate clearance interval with major specificity and sensitivity to predict mortality. Different lactate clearance cuts were taken (<0%, 1-50%, >51%) to find its specificity and sensitivity, as well as positive and negative predictive Value (SPSS v. 17).

Table 1. Patient's characteristics

Age	*63.95±14.5 (26-87)*
Woman	*22(53.7)*
Man	*19(46.3)*
Mortality	*10(24.4)*
Septic shock	*12(29.2)*
Hypovolemic shock	*26(63.4)*
Grade 1	*10(24.3)*
Grade 2	*11(26.8)*
Grade 3	*5(12.1)*
Grade 4	*0*
Cardiogenic shock	*3(7.3)*
Initial lactate	*5.66±3.66*
Lactate clearance (6 h)	*5.54±3.76*
Lactate clearance (12 h)	*4.53±3.19*
Lactate clearance (24 h)	*3.61±3.25*
APACHE II (admission)	*14±5.99*
APACHE II (24 h)	*9.36±6.04*
PCO_2 <32 mmHg	*25(61)*

RESULTS

A 41 patients total were included in the study on a period of 6 months, 22 (53.7%) women and 19 (46.3%) men, mean age 63.95 years (ranging from 26 to 87 years). The time of observation was of 24 hours. The septic shock diagnostic were on 12 (29%) patients, hypovolemic shock on 26 (63.4%) patients and cardiogenic shock on 3 (7.3%) patients. The general patient's characteristics, types of shock, initial lactate, lactate clearance, and APACHE II, admitted on this study are shown on Table 1. The relation of lactate levels at 6, 12 and 24 hours after admission of patients with the type of shock is shown in the Figure1. The APACHE II score at admission of patients and at 24 hours after admission was of 14±5.99 and 9.36±6.04 respectively, the relation between APACHE II and type of shock is shown in the Figure 2. Values of lactate clearance at 6, 12 and 24 hours were compared with the 3 types of shock state included in this paper, as shown in Figure 3. Inferential statistics on the age, type of shock, APACHE II score, vital signs, results of laboratory and lactate clearance was made in survivors and not survivors. We found statistically significant difference in the variables: APACHE II at 24 hours, lactate clearance at 6, 12 and 24 hours, hypovolemic shock, cardiogenic shock, vasopressor use and lactate values at 12 and 24 hours among survivors and not survivors (t Student and Mann Whitney U univariate analysis). Lactate clearance at 6, 12, 24 hours among survivors and not survivors demonstrated statistical significance in the univariate analysis ($p<0.002$, $p<0.000$, $p<0.000$) respectively. A statistically significant value was obtained on the clearance measure at 12 and 24 hours (Multivariate Analysis) (Table 2).

Table 2. Multivariate analysis. Variables associated with hospital mortality

Variable	*p value*
Hypovolemic shock	*0.000*
Cardiogenic shock	*0.830*
APACHE II (24 h)	*0.000*
Lactate clearance (6 h)	*0.514*
Lactate clearance (12 h)	*0.002*
Lactate clearance (24 h)	*0.000*

The ROC curve for the prediction of mortality of the different measures of lactate clearance, are shown in the Figure 4. In the ROC curve the cutoff point with greater sensitivity and specificity on the lactate clearance at 24 hours after admission, could not be determined.

Table 3. Sensitivity, specificity, positive predictive value and negative predictive value of death in the emergency room for different breakpoints debugging lactate at 24 hours.

Cutoff point	*PPV*	*NPV*	*Sensitivity*	*Specificity*
Lactate clearance at 24 h <0	*80*	*0*	*80*	*0*
Lactate clearance at 24h 1-50	*13*	*79*	*20*	*70*
Lactate clearance at 24 h >51	*0*	*75*	*0*	*79*

PPV: Positive Predictive Value, NPV: Negative Predictive Value.

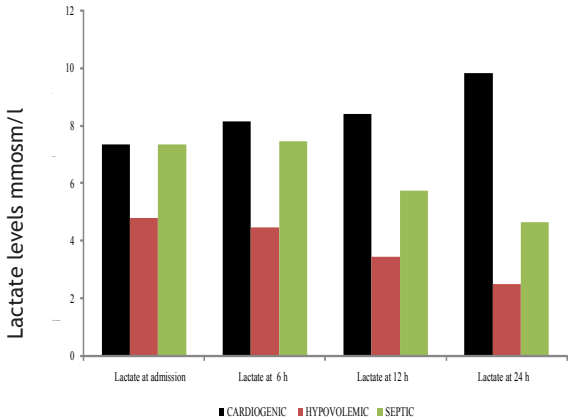


***Figure 1**. Comparison between types of shock and lactate levels at admission, at 6, 12 and 24 h.*

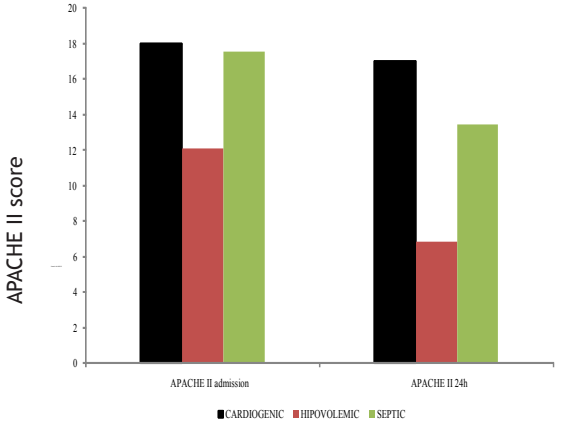


***Figure 2**. Comparison between type of crash and points of APACHE II on admission and 24 h in patients*

For that reason, 3 arbitrary cutoff points were taken, being these at <0%, 1-50% and at >50% to determine sensitivity and specificity, as well as its positive and negative predictive value (Table 3). The positive predictive value of lactate clearance to mortality in a cutoff point of minor than 0 at the 24 hours after admission is of 80% with a sensitivity of 80%, therefore we can conclude that is the best cutoff point to predict mortality. Besides, a specificity of 79% to mortality on the group that cleared more than 50% at the 24 hours of admission was found. As well as that from the 10 patients that died, 8 did not cleared lactate and 2 cleared less than 50%. While granulation tissues were detected around the ostium in 10 patients to whom applications were performed with a partial success, the cause of the partial failure of 4 cases could not be explained completely.

DISCUSSION

Shock state is a common condition in the emergency room service. Tissue perfusion is altered, as well as lactate blood levels; therefore this is a good predictor for mortality in patients on shock state. However, it is more exactly the measure of its clearance. Measuring lactate at admission among survivors and non-survivor's patients, lactate concentration is major in the non survivors group, however, it was not statistically significant in the multivariate analysis. Similar results were obtained by Porras and Ige (9). In septic shock lactate clearance has not been studied (18).

Patients in cardiogenic shock increased its lactate levels through time, which suggest that this is related with a clearance deficiency of this molecule. About this argument we cannot mention articles written, because the majority had focused on septic shock. On the study of Revelly et al. (12) it is commented that patients with cardiogenic shock have a rise in lactate production, but are able to maintain its clearance, which differs from our study. Our sample is small; therefore it had not a statistical significance in the multivariate analysis (11-16).

In the case of patients diagnosed with hypovolemic and septic shock, lactate levels decreased through time, which indicate, they response better to the treatments performed in the emergency room service (Figure 1). In the case of cardiogenic shock patients, we observed an increased on lactate levels of 2.5%, but not in the patients with hypovolemic and septic shock in which a decreased in lactate levels were observed on a 2.31 and 2.61% respectively (n:41).

Patients with hypovolemic shock increased lactate clearance levels since the first measure performed (6 hours) (13). Initially (admission and measure at 6 hours) patients in septic shock did not showed clearance in the lactate levels. However, from 12 hours increased its clearance levels in relation with time (17). Besides, mortality was determined in patients after 24 hours of admission in relation to the type of shock studied. In this analysis we observed which type of shock repre-

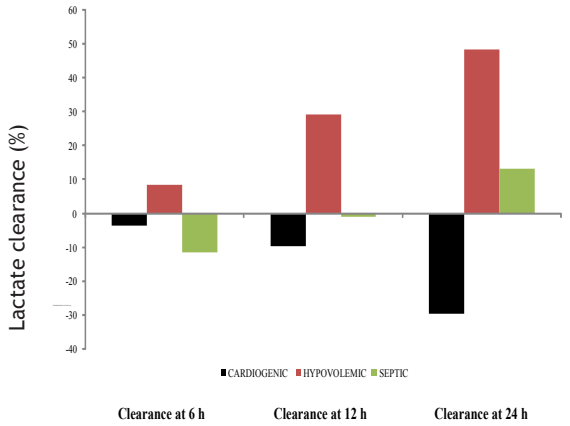
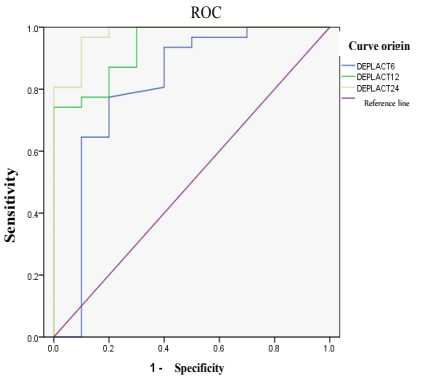


***Figure 3**. Comparison between Types of Shock and Lactate Clearance at 6, 12 and 24 hours of admission in patients in the Emergency Room at Hospital General Regional No. 36.*



Contrast variable results	Area under the curve	Statistical significance
Clearance at 6 h	0.619	.004
Clearance at 12 h	0.864	.000
Clearance at 24 h	0.935	.000

*La variable de resultado de contraste: DEPLACóltiene al menos un empate entre el grupo de estado real positivoy el grupo de estado real negativo. Losestadísticos pueden estar sesgados.
Hipótesisnula: área verdadera = 0,5

***Figure 4**. ROC curve for the distribution of the results for Lactate Clearance at 6, 12 and 24 hs in relation to Mortality after 24 hours of admission to the Emergency Room of Hospital General Regional No. 36.*

sents the major mortality, being this cardiogenic shock, because 100% of patients presenting this diagnostic died. This data presents a clear correlation with lactate clearance, because all patients in cardiogenic shock increased its lactate levels through time, meaning there was not clearance. Patients in hypovolemic shock had the fewest mortality percentage, which is related to the best lactate clearance levels. Finally, for septic shock, mortality represented the 33.33% and lactate clearance presented acceptable levels after 12 hours of admission (Figure 4).

It is important to mention the relation kept with the proportioned treatment. In the Hospital General Regional No. 36 from the Instituto Mexicano del Seguro Social, we have a better possibility to successfully treat the hypovolemic and septic shock, on the sense of secure volemia for better tissue perfusion, guaranteeing with it a major lactate clearance, therefore a better prognostic for the patient. In patients with cardiogenic shock we observed a light decreased on the APACHE II score, this decrement was more evident in the patients cursing with hypovolemic and septic shock.

The interpretation of one lactate value or measure of clearance at 6 hours has many limitations. First, measure of lactate at admission reflects a concentration of the resulting, between production and elimination and not of established therapeutic management.

It is probably because there is not a response from the patient to the treatment, yet. We observed that lactate clearance at the 24 hours after admission, has a major statistically significant association than that found at 6 and 12 hours, showing that sustained time of clearance lactate predicts mortality better. Bryan et al. (3) found as well significant statistical, but did not find mortality association to APACHE II, although, we did find it in the multivariate analysis. In the work of Levraut et al. (4), specificity and sensitivity are mentioned similar to the one found by us for the association of clearance lactate and Mortality, although in that work mentioned at 28 days. It was determined by the ROC curve, that the percentage of lactate clearance with the best value to predict mortality is the one measured at the 24 hours. However, the percentage measured at the 12 hours presented as well a good predictive value (Figure 4).

The ROC curve provides a global representation of the diagnostic accuracy. The curve shown is crescent, characteristic that reflects commitment between sensitivity and specificity; if the cutoff point value is to be modified to obtain major sensitivity, it can only be on expense of diminishing the specificity at the same time.

The accuracy of the test, rises as the curve moves form the diagonal to the left upper vertex, so is easy to observe that the test with better predictive value of mortality is the lactate clearance at the 24 hours, followed by the lactate clearance at the 12 hours. The data of the area beneath the curve are shown, which are indicative of a better predictive value as well, the higher the value of this item, the better the test to predict a condition, (mortality on this scenario). We could consider that goals of resuscitation such as vital signs should incorporate the value of lactate clearance as mentioned by Bryant et al. (3) to better evaluate the response to the therapy given and determine the prognosis of mortality of patients in our service.

Based on the findings in this study we can conclude that the determination of lactate clearance at 12 and mostly 24 hours is a predictor of mortality in patients in shock state.

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