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Hyperlactatemia and the Importance of Repeated Lactate Measurements in Critically Ill Patients

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ABSTRACT

Objective. The aim of the study was to describe the prevalence of hyperlactatemia and emphasis on repeated lactate measurements in critically ill patients, and the associated mortality. **Materials and methods.** The study included 70 patients admitted in the Medical Intensive Care Unit at the Clinical Center, University of Sarajevo, in a 6-month period (July - December 2015). The following data were obtained: age, gender, reason for admission, Simplified Acute Physiology Score II, Acute Physiology and Chronic Health Evaluation, lactate concentrations upon admission, after 24 and 48 hours, and outcome (discharge from hospital or death). **Results.** Upon admission,hyperlactatemia was present in 91.4% patients with a mean concentration of lactate 4.13 ±1.21 mmol/L. Lactate concentration at 48 hours was independently associated within creased in-hospital mortality (P = 0.018). **Conclusion.** Persistent hyperlactatemia is associated with adverse outcome in critically ill patients. Lactate concentration at 48 hours is independently associated within creased in-hospital mortality and it represents a statistically significant predictive marker of fatal outcomes of patients. Blood lactate concentrations > 2.25 mmol/L should be used by clinicians to identify patients at higher risk of death. **Keywords: hyperlactatemia, critical illnesses, fatal outcomes.**

1. INTRODUCTION

In physiological conditions, about 1500 mmol of lactate is produced daily from various organs, including the muscles, intestine, red blood cells, brain and skin (1). Lactate is metabolized by the liver (about 60 %), the kidneys (about 30 %), and other organs. Normal blood lactate concentration is around 1 mmol/L (2).One of the most important metabolic changes due to lack of oxygen is the Pasteur effect (3). Due to oxygen shortage, pyruvate derived from the anaerobic conversion of glucose cannot enter the Krebs' cycle via acetyl-coenzyme A to produce energy (3). The conversion of pyruvate to lactate allows energy production without oxygen (3). This is the most important adaptive mechanism to survive hypoxia (3).

Hyperlactatemia is defined as a lactate measurement > 2 mmol/L, and is common in critical illness (4). Lactate should not be regarded as toxic or harmful by itself. Although frequently used to diagnose in adequate tissue oxygenation, other processes not related to tissue oxygen at ion may increase lactate levels (4). Especially in critically ill patients, increased glycolysis maybe an important cause of hyperlactatemia (5). Hyperlactatemia has been described as a hallmark characteristic of shock states (6). The metabolism of lactate in critically ill patients has also been associated with cellular inflammatory response (7). Repeated lactate measurements over time may be more useful for clinicians rather than a single lactate measurement for risk stratification in critically ill patients. Although the suggested optimal timing of lactate measurements is not precisely defined, the importance of repeated lactate measurements in critically ill patients is based on a time window in which the hypoxic cells return to a normal state if oxygen is supplied. Some studies reported that 6-hourly changes could be a useful guide (8, 9) while other suggest longer time intervals of 12–24 hours (10, 11). his time frame is the opportunity for the patient to receive treatment to save the cells and organs from irreversible damage.

2. OBJECTIVE

The aim of the study was to describe the prevalence of hyperlactatemia and emphasis on repeated

lactate measurements in critically ill patients, and the associated mortality.

3. MATERIAL AND METHODS

Ninety-four patients were admitted to the 7-bed Medical Intensive Care Unit, Clinical Center, University of Sarajevo, between July and December 2015. Of these, 12 patients died within 24 hours of admission, and another 12 patients were excluded from the study due to incomplete laboratory data. The remaining 70 patients were included in the study. The patients were admitted from the emergency department or from a hospital ward. The reasons for admission were grouped in to five diagnoses: sepsis/septic shock, cardiogenic shock, respiratory failure, neurological and other causes. When multiple diagnoses were present, the leading one with the worst prognosis was selected as the main reason for admission. For each patient, the following data were collected: age, gender, Simplified Acute Physiology Score (SAPS) II, Acute Physiology and Chronic Health Evaluation (APACHE) II, lactate concentrations upon admission, after 24 and 48 hours, and at the clinical outcomes. Based on the clinical outcomes, patients were divided into two groups: survivors, a) patients who were discharged from the hospital, and b) non-survivors, i.e. patients who died during the hospitalization.

Statistical analyses were performed retrospectively and anonymously. Routine collection of data did not interfere with patient care and treatment in any way. Data were tabulated for continuous variables as means and standard deviation, and for categorical variables as absolute and relative frequencies. Logistic regression was done with lactate concentration categorical variable as the outcome measure in a single regression analysis. ANOVA test was performed for repeated lactate measurements at 0h, 24h and 48h. A receiver operating characteristic (ROC) curve was used to determine a cut-off value for the sensitivity and specificity of lactate concen-

tration for prediction of mortality. Statistical significance was p ≤ 0.05. Graphically, data were presented in tables and figures. Data were analyzed using SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA).

3. RESULTS

Out of 70 patients included in the study, there were 44 (62.9%) survivors and 26 (37.1%) non-survivors. Baseline patient characteristics and survival prediction scores are presented in Table 1. Hyperlactatemia (serum lactate > 2 mmol/L) upon admission was present in 64 (91.4%) of the admitted patients, with mean lactate concentration 4.13 ±1.21 mmol/L. The reasons for admission and lactate concentrations at admission are presented in Table 2. Mean lactate level values in survivors and non-survivors are presented in Table 3. By using Anova test, the statistically significant difference was established in the mean lactate values at 0h, 24h and 48h between survivors and non-survivors.

	Survivors (n=44)	Non-survivors (n=26)	P
Age (years)	59.1±18.2	66.5±16.4	0.094
Malespatients, n (%)	16 (36.3)	11 (42.3)	0.766
SAPS II	43.1±11.5	64.5±16.8	0.0001
APACHE II	19.4±7.2	28.0±8.3	0.0001

Table 1. Baseline patient characteristics and survival prediction scores

Reasonsforadmission	Patients, n (%)	Meanlactateconcentration (mmol/L)
Sepsis / septicshock	16 (22.9)	5.01 ±2.19
Cardiogenicshock	15 (21.4)	5.91 ±1.94
Respiratoryfailure	24 (34.3)	3.42 ±0.7
Neurologicalcauses	10 (14.3)	2.72 ±0.93
Othercauses	5 (7.1)	3.61 ±1.44

Table 2. Reasons for admission into the medical ICU and lactate measurements at admission.

		N	Mean (mmol/L)	SD	SEM	95% Confidence Interval for Mean		Minimum (mmol/L)	Maximum (mmol/L)
						Lower Bound	Upper Bound		
LAC 0h	Survivors	44	3,64	1,60	,24	3,1596	4,1359	1,10	8,10
	Non-survivors	26	4,88	2,78	,54	3,7626	6,0143	1,10	11,30
	F=5.608; p=0.021								
LAC 24h	Survivors	39	2,40	1,49	,23	1,9169	2,8883	,70	8,20
	Non-survivors	23	4,00	2,76	,57	2,8085	5,2001	,70	12,00
	F=8.784; p=0.004								
LAC 48h	Survivors	38	1,50	,52	,08	1,3281	1,6719	,60	2,50
	Non-survivors	18	3,54	2,39	,56	2,3543	4,7345	1,40	9,80
	F=25.649; p=0.001								

Table 3. Comparisonofmeanlactatelevels at 0h, 24h and 48h betweensurvivorsandnon-survivors. LAC= lactate concentration

		B	S.E.	Wald	df	Sig.	Exp(B)	95% CI, EXP(B)	
								Lower	Upper
Step 1a	LAC 0h	,131	,207	,401	1	,527	1,140	,760	1,711
	LAC 24h	,108	,283	,145	1	,704	1,114	,639	1,941
	LAC 48h	1,900	,803	5,606	1	,018	6,689	1,387	32,252
	Constant	-5,452	1,575	11,977	1	,001	,004		

Table 4.Effectofthelactatevalues on thepatientoutcome LAC= lactate concentration
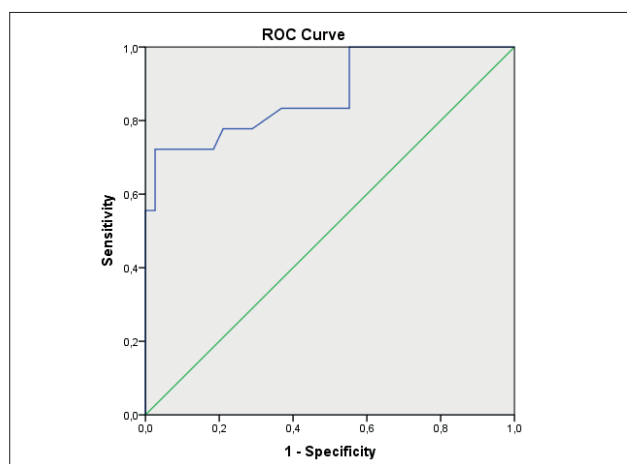
Figure 1. The receiver operating curve for lactate measurements at 48 hours after ICU admission, for predicting fatal clinical outcome.

To evaluate the effect of the lactate values on the patient outcome, regression analysis was used (Table 4).

Lactate concentration at 48 hours was independently associated with increased in-hospital mortality (OR 6.68, 95% (CI) 1.38 to 32.25, P = 0.018). Further analysis showed that lactate concentration at 48 hours represents a statistically significant predictive marker of fatal outcomes of patients (area under the curve of 0.874, CI 0.769-0.980 p = 0.001) (Figure 1). The cut-off value for LAC 48h was 2.25 mmol/L, with sensitivity of 0.722 and specificity of 0.921.

4. DISCUSSION

In our study, the mortality rate of critically ill patients, admitted to the medical ICU, was 37.1%, which is similar to or lower than the mortality rate reported in previous studies (12). Upon admission, hyperlactatemia was present in 91.4% of critically ill patients. Previous studies investigated the impact of hyperlactatemia on mortality in patients admitted to the ICU, and reported cumulative prevalence rates of 10 to 70% (13, 14). Such a high occurrence of hyperlactatemia at admission in the patients in our study might be explained by the possibility that they were admitted to the ICU at a more advanced stage in their clinical conditions.

In our study, the mean lactate concentration upon admission was 4.13 ±1.21 mmol/L in critically ill patients. A previous study showed that an initial lactate level of more than 4.0 mmol/L substantially increases the probability of acute-phase death (15). Kliegel et al. showed that their survivors had lower lactate levels on admission than that found in our study (16). In our study, patients with sepsis/septic shock had a mean lactate concentration of 5.01 ±2.19 mmol/L. Haas et al. found that the degree of hyperlactatemia was directly related to the severity of the shock state and to mortality rates (17). Previous studies in patients with sepsis confirmed the impact of persistent hyperlactatemia on the poor clinical outcomes (18, 19). Patients that with cardiogenic shock had a mean lactate concentration of 5.91 ±2.40 mmol/L. Previous studies in patients with cardiogenic shock showed that lactate concentrations decreased more in survivors than

in non-survivors (20, 21). Increased lactate concentrations may be due to other factors than just cellular hypoxia (22). Use of beta-adrenergic stimulation may contribute to increased lactate production (22).

In our study, there was statistically significant difference in the mean lactate concentration at admission, after 24 hours and 48 hours between survivors versus non-survivors. Our results are consistent with those reported by Mikkelsen et al. (23). In spite of prevailing evidence that the lactate reduction influences the critically ill patient outcomes, there are five studies reporting no predictive effect of a decrease in lactate levels over time on mortality (24, 25, 26, 27, 28). Although they showed no effect on mortality, the study by Manikis et al (24) and Billeteret al (25) suggested a relationship between lactate concentration and morbidity outcomes.

In our study, lactate levels at 48 hours were the independent predictor for mortality, with a cut-off value of 2.25 mmol/L, and sensitivity of 72.2 % and specificity of 92.1%. The study by Kliegel et al. also showed that lactate concentration at 48 hours was an independent predictor for mortality. In their study, lactate levels higher than 2 mmol/Lafter 48 hours predicted mortality, with a specificity of 86% and sensitivity of 31% (16). The measurements of lactate concentration were spaced 24 hours apart (0h, 24h, 48h). Several studies report that a shorter time frame, ie. every six hour intervals in lactate concentration, could be a more accurate clinical guide (29, 30). In the study by Haas et al, lactate elimination after 12 h showed a good predictive effect on mortality in the ICU. In that study, the ICU patients whose lactate elimination was at 32.8%, had a mortality rate of 96.6% (17). Our study was observational, and as such did not include the effect of therapeutic interventions on the lactate kinetics. An interventional trial by Jansenet al. targeted a lactate decrease of at least 20 % in 2 hours for the initial 8 hours of treatment in ICU patients with an initial lactate concentration of≥ 3 mmol/L. This strategy was associated with a lower mortality rate for the lactate-guided therapy (31). In another interventional study, the patients were managed according to the same protocol by reducing lactate levels to <2.4 mmol/L. Failure to achieve this target was associated with an increased risk of infection, length of hospital stay, and mortality (32). Measuring blood lactate to assess the efficacy of therapy has also been shown by Rivers et al (33). A rapid rate of lactate elimination and an earlier time of resolution of hyperlactatemia has been associated with increased survival rate (34). Although changes in blood lactate kinetics were clearly significant after 6 hours in many studies and after 12 hours in most, it is currently not clear what the best time interval between lactate measurements should be. A decrease in blood lactate following a therapeutic intervention is a major indicator of the efficacy of the treatment. This means that repeated lactate measurement may be used as a guide to therapy. If blood lactate concentrations do not normalize over time, the need for alternative therapy should be considered.

Limitations of the study. Our relatively small sample size and being a single center study were limiting factors.

Advantages of the study. This study offers several advantages, including an objective basis for repeated measurements of blood lactate concentration and its impact on the clinical outcomes, especially focusing on critically ill patients. In our country not so much research in this field.

5. CONCLUSION

Blood hyperlactatemia is common in critically ill patients and at 48 hours is independently associated with an increase in mortality in hospitals and it represents a statistically significant predictive marker of fatal clinical outcomes for critically ill patients. Blood lactate concentrations> 2.25 mmol/L can be regarded by clinicians to identify patients at high mortality risk.

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- **Conflict of interest**: none declared..

REFERENCES

1. Levy B. Lactate and shock state: the metabolic view. Curr Opin Crit Care. 2006; 12(4): 315-21.
2. Nichol AD, Egi M, Pettila V, Bellomo R, French C, Hart G, et al. Relative hyperlactatemia and hospital mortality in critically ill patients: a retrospective multi-centre study. Crit Care. 2010; 14(1): R25.
3. Leverve XM, Mustafa I. Lactate: a key metabolite in the inter cellular metabolic interplay. Crit Care. 2002; 6(4): 284-5.
4. Rishu AH, Khan R, Al-Dorzi HM, Tamim HM, Al-Qahtani S, Al-Ghamdi G. et al. Even mild hyperlactatemia is associated with increased mortality in critically ill patients. Crit Care. 2013; 17(5): R197.
5. Bakker J, Nijsten MW, Jansen TC. Clinical use oflactate monitoring in criticallyill patients. Ann Intensive Care. 2013; 3(1): 12.
6. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med. 2014; 40(12): 1795-815.
7. Kellum JA, Song M, Li J. Lactic and hydrochloric acids induce different patterns of inflammatory response in LPS-stimulated RAW 264.7 cells. Am J Physiol Regul Integr Comp Physiol. 2004; 286(4): R686-92.
8. Puskarich MA, Trzeciak S, Shapiro NI, Arnold RC, Heffner AC, Kline JA, et al. Prognostic value and agreement of achieving lactate clearance or central venous oxygen saturation goals during early sepsis resuscitation. Acad Emerg Med. 2012; 19: 252-8.
9. Zanaty OM, Megahed M, Demerdash H, Swelem R. Delta neutrophil index versus lactate clearance: early markersfor out come prediction in septic shock patients. Alex J Med. 2012; 48: 327-33.
10. Cerovic O, Golubovic V, Spec-Marn A, Kremzar B, Vidmar G. Relationship between injury severity and lactate levels in severely injured patients. Intensive Care Med. 2003; 29: 1300-5.
11. Roumen RM, Redl H, Schlag G, Sandtner W, Koller W, Goris RJ. Scoring systems and blood lactate concentrations in relation to the development of adult respiratory distress syndrome and multiple organ failure in severely traumatized patients. J Trauma. 1993; 35: 349-55.
12. Sánchez-Casado M, Hostigüela-Martín VA, Raigal-Caño A, Labajo L, Gómez-Tello V, Alonso-Gómez G et al. Predictive scoring systems in multiorgan failure: A cohort study. Med Intensiva. 2016; 40(3): 145-53.
13. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med. 2004; 32(8): 1637-42.
14. Kaplan LJ, Kellum JA. Initial pH, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular injury. Crit Care Med. 2004; 32(5): 1120-4.
15. Trzeciak S, Dellinger RP, Chansky ME, Arnold RC, Schorr C, et al. Serum lactate as a predictor of mortality in patients with infection. Intensive Care Med. 2007; 33(6): 970-7.
16. Kliegel A, Losert H, Sterz F, Holzer M, Zeiner A, Havel Cet al. Serial lactate determinations for prediction of outcome after cardiac arrest. Medicine. 2004; 83(5): 274-9.
17. Haas SA, Lange T, Saugel B, Petzoldt M, Fuhrmann V, Metschke M, et al. Severe hyperlactatemia, lactate clearance and mortality in unselected critically ill patients. Intensive Care Med. 2016; 42(2): 202-10.
18. Ha TS, Shin TG, Jo IJ, Hwang SY, Chung CR, et al. Lactate clearance and mortality in septic patients with hepatic dysfunction. Am J Emerg Med. 2016; 34(6): 1011-15.
19. Bolvardi E, Malmir J, Reihani H, Hashemian AM, Bahramian M, Khademhosseini P, et al. The role of lactate clearance as a predictor of organ dysfunction and mortality in patients with severe sepsis. Mater Sociomed. 2016; 28(1): 57-60.
20. Attana P, Lazzeri C, Chiostri M, Picariello C, Gensini GF, Valente S. Lactate clearance in cardiogenic shock following ST elevation myocardial infarction: a pilot study. Acute Card Care. 2012; 14(1): 20-6.
21. Park TK, Yang JH, Choi SH, Song YB, Hahn JY, Choi JH, et al. Clinical outcomes of patients with acute myocardial infarction complicated by severe refractory cardiogenic shock assisted with percutaneous cardiopulmonary support. Yonsei Med J. 2014; 55(4): 920-7.
22. Qvisth V, Hagstrom-Toft E, Enoksson S, Bolinder J. Catecholamine regulation of local lactate production in vivo in skeletal muscle and adipose tissue: role of -adrenoreceptor subtypes. J Clin Endocrinol Metab. 2008; 93(1): 240-6.
23. Mikkelsen ME, Miltiades AN, Gaieski DF, Goyal M, Fuchs BD, Shah CV, et al. Serum lactateisassociatedwithmortality in severesepsisindependentof organ failureandshock. Crit Care Med. 2009; 37(5): 1670-7.
24. Manikis P, Jankowski S, Zhang H, Kahn RJ, Vincent JL. Correlation of serial blood lactate levels to organ failure and mortality after trauma. Am J Emerg Med. 1995; 13: 619-22.
25. Billeter A, Turina M, Seifert B, Mica L, Stocker R, Keel M. Early serum procalcitonin, interleukin-6, and 24-hr lactateclearance: useful indicators of septic infections in severelytraumatized patients. World J Surg. 2009; 33: 558-66.
26. Starodub R, Abella BS, Grossestreuer AV, Shofer FS, Perman SM, Leary M, et al. Associationof serum lactate and surviva loutcomes in patients undergoing therapeutic hypothermia after cardiac arrest. Resuscitation. 2013; 84: 1078-82.
27. Freitas AD, Franzon O. Lactate as predictor of mortality in polytrauma. Arq Bras Cir Dig. 2015; 28: 163-6.
28. Amir A, Saulters KJ, Olum S, Pitts K, Parsons A, Churchill C et al. Outcomes of patients with severe sepsis after the first 6 hrs of resuscitation at a regional referral hospital in Uganda. J Crit Care. 2016; 33: 78-83.
29. Puskarich MA, Trzeciak S, Shapiro NI, Albers AB, Heffner AC, Kline JA, et al. Whole blood lactate kinetics in patients undergoing quantitative resuscitation for severe sepsis and septic shock. Chest. 2013; 143(6): 1548-53.
30. Walker CA, Griffith DM, Gray AJ, Datta D, Hay AW. Early lactate clearance in septic patients with elevated lactate levels admitted from the emergency department to intensive care: time to aim higher? J Crit Care. 2013; 28(5): 832-7.
31. Jansen TC, van Bommel J, Schoonderbeek FJ, SleeswijkVisser SJ, van derKlooster JM, Lima AP, et al. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. Am J Respir Crit Care Med. 2010; 182: 752-61.
32. Claridge JA, Crabtree TD, Pelletier SJ, Butler K, Sawyer RG, Young JS. Persistent occult hypo perfusionis associated with a significant increase in infection rate and mortality in major trauma patients. J Trauma. 2000; 48: 8-14.
33. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B. et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001; 345(19): 1368-77.
34. Husain FA, Martin MJ, Mullenix PS, Steele SR, Elliott DC. Serum lactate and base deficit as predictors of mortality and morbidity. Am J Surg. 2003; 185(5): 485-91.