Med & Health 2014; 9(2): 124-133

ORIGINAL ARTICLE

The 28-Day Mortality Prediction in Sepsis Patients Using Static Lactate Concentration and Early Lactate Clearance: An Observational Study

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ABSTRAK

Sepsis menyebabkan kadar kematian dan morbiditi pesakit di hospital yang tinggi. Kepekatan laktat statik dan kadar pengurangan paras laktat awal dicadangkan sebagai faktor utama penentuan kadar kematian pesakit sepsis. Kajian ini mengaplikasikan kepekatan laktat dan kadar pengurangan paras laktat pada tempoh enam jam pertama di Jabatan Kecemasan untuk meramalkan kadar kematian pesakit sepsis selepas 28 hari. Pesakit yang menghidapi sepsis, sepsis teruk dan renjatan sepsis yang menerima rawatan di jabatan kecemasan Universiti Kebangsaan Malaysia akan dimasukkan dalam kajian ini. Kepekatan laktat static darah pesakit pada masa permulaan kemasukan pesakit, pada satu jam dan pada enam jam akan dikaji. Pesakit kemudiannya diberi rawatan yang berpatutan mengikut diagnosis sepsis, iaitu rawatan piawai atau rawatan awal berasalkan sasaran untuk sepsis. Selepas 28 hari, pesakit akan dihubungi melalui telefon, emel atau laporan perubatan pesakit. Kemudian, pesakit akan dikatogorikan kepada golongan yang hidup atau mati. Dalam kajian ini, kepekatan laktat menujukan hubung kait yang erat dengan golongan yang mati berbanding dengan golongan yang hidup dalam ketiga-tigaan masa, iaitu jam 0, 1 dan 6 ($p<0.05$). Akan tetapi, kadar pengurangan paras laktat tidak menunjukkan sebarang hubung kait dengan kadar kematian pesakit selepas 28 hari. Kesimpulannya, kepekatan laktat static merupakan petunjuk yang baik untuk meramalkan kadar kematian sepsis berbanding dengan kadar pengurangan paras laktat. Walaupun kadar pengurangan paras laktat tidak dapat membuktikan sebarang hubung kait dengan kadar kematian selepas 28 hari, kajian kami menunjukkan ia masih boleh dimanfaatkan sebagai pemantau yang baik semasa merawat pesakit sepsis.

Kata kunci: sepsis, paras laktat, kadar pengurangan laktat, kadar kematian

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ABSTRACT

Sepsis causes high mortality and morbidity. Static lactate concentration and early lactate clearance are cited to be a predictor for sepsis survival. This study examined the clinical utility of static lactate concentration and early lactate clearance within the first six hours of admission in Emergency Department (ED) to predict 28-day mortality rate in sepsis patients. Patients who presented with sepsis, severe sepsis or septic shock and admitted to ED of Universiti Kebangsaan Malaysia Medical Centre were recruited. Blood lactate concentrations were measured upon admission (H0), at 1st hour (H1) and 6th hour (H6), respectively. Either standard treatment of sepsis or early goal directed therapy was initiated according to sepsis severity. A follow-up report was conducted at 28 days via telephone call, e-mail or case notes. Patients were later classified into survivor and non-survivor as final outcome. Static lactate concentration appeared to be significantly higher for non-survivor as compared to the survival group at H0, H1 and H6 ($p<0.05$). The lactate clearance trend reflects no relationship between early lactate clearance and 28-day mortality. Static lactate concentration showed a superior predictor for sepsis over early lactate clearance. Although early lactate clearance was unable to prove its ability to predict 28-day mortality, our findings suggest it can be a useful tool to gauge the resuscitation outcome.

Keywords: sepsis, lactate levels, lactate clearance, mortality

INTRODUCTION

Early identification and treatment of sepsis are essential to improve the outcome of sepsis patient or patient with impending sepsis (Rivers et al. 2001; Shapiro et al. 2005). Static lactate elevation had been utilized as a key to predict mortality rate of sepsis patients in emergency department (ED) (Bakker et al. 1991; Aduen et al. 1994; Bakker et al. 1996; Bakker 2001; Dellinger et al. 2004a; Varpula et al. 2005; Marty et al. 2013). Current Surviving Sepsis Campaign (Dellinger et al. 2004b; Nguyen et al. 2004) advocates measurement of lactate in sepsis patient and possible severe sepsis patient to guide the further management (Shapiro et al. 2005). On the other hand, an early lactate clearance had also shown improvement in the outcome of sepsis as well (Fuller & Dellinger 2012; Walker et al. 2013) and few other studies had shown its prognostic outcome (Varpula et al. 2005; Fuller & Dellinger 2012; Puskarich et al. 2012). Furthermore, lactate clearance has been proposed as a better therapeutic guidance for severe sepsis and septic shock patient's management (Kruse 1999; Shapiro et al. 2005; Wang et al. 2006; Jones et al. 2010; Jansen et al. 2010; Jones 2011). Lactate clearance also suggested being less invasive and more cost effective in treating sepsis (Varpula et al. 2005). However, some studies had point out the flaw of static lactate and lactate clearance as risk stratification. Many

sepsis patients are presented with normal static lactate (Mizock 2001; Dugas et al. 2009; Hernandez et al. 2011). Static lactate level is inconsistent with fluctuation after intervention (Hernandez et al. 2011, Rivers et al. 2011). However, a research has found out that lactate clearance does not improve the outcome in septic syndrome patients (Jones et al. 2010). Another study also proposed that lactate clearance should not be used as a substitute guideline for management severe sepsis and septic shock with reasons that inconsistency of static lactate is inappropriate risk stratification and lactate clearance can be a delayed indicator of tissue perfusion with lack of understanding on mechanism behind it (Marty et al. 2013). In addition, better lactate clearance does not necessary improved outcome of septic syndrome patient (Marik & Bellomo 2013). These arguments had triggered us to elucidate (a) the association of static lactate and lactate clearance at 0 hour, 1 hour and 6 hour, respectively with 28-day mortality in sepsis syndrome of the ED and (b) to examinine for 28-day mortality prognostication of static lactate level and first six hours lactate clearance during admission in ED for sepsis syndromes.

MATERIALS AND METHODS

SETTING AND STUDY DESIGN

This was a prospective observation study which was performed in ED of Universiti Kebangsaan Malaysia Medical Centre (UKMMC) from March 2014 to May 2014. The study population consisted of severe sepsis, septic shock and sepsis patients who were admitted in ED during the study. The initial venous or arterial blood serum lactate level at 0 hour, 1st hour and 6th hour were measured. After 28 days, a follow-up was pursued in each patient to determine all-cause mortality.

PARTICIPANTS

The inclusion criteria were consented patients, suspected sepsis patients who older than 17-year-old with two or more criteria of systemic inflammatory response syndrome. Besides that, patients with systolic blood pressure (SBP) less than 90 mmHg after 500 to 1000 ml crystalloid fluid challenge also recruited in our study. However, the exclusion criteria are the patients who were partially treated with antibiotics for more than three days, or patient deceased during the period of recruitment. Patient transferred out to other hospitals without completing the six hours management were also excluded from this study.

VARIABLES

Sepsis is defined as infection with two or more criteria of Systemic Inflammatory Response Syndrome (SIRS). In addition, definition of severe sepsis is sepsis associated with at least one tissue hypo-perfusion or present of sepsis-induced organ dysfunction. Furthermore, septic shock which is also known as hypotension induce by sepsis is defined with a mean arterial pressure < 70 mm Hg or a SBP decrease more than 40 mm Hg or < 2 SD below normal, or systolic blood pressure (SBP)

less than 90 mm Hg for age, which there is no other causes responsible for the hypotension despite adequate fluid resuscitation. Moreover, the definition of sepsis induced tissue hypo-perfusion is oliguria, septic shock, or elevated lactate (Table 1). Lactate clearance is defined as blood lactates reduced by 10% or more from the initial blood lactate levels. It can be calculated by using the formula as follows:

$[(LAC_{initial} - LAC_{final})/ LAC_{initial}] \times 100\%]$

STUDY SOURCES/ MEASUREMENT

Once the patient has fulfilled the inclusion and exclusion criteria, blood lactate was withdrawn (2 ml) at H0, H1 and H6. The samples were collected into sodium fluoride/ potassium oxalate (grey top) test tube. After that, the blood was centrifuged (1300G, 10 minutes) and sent for lactate analysis. A standard treatment of sepsis was initiated at 0 hour for patients who were identified as sepsis. For sepsis-induced hypo-perfusion patients, they were treated

Table 1: Definition of sepsis, severe sepsis, septic shock and sepsis induced hypoperfusion

Definition	
Sepsis	**SIRS criteria (2 or more) + a source of infection**
	1. Temperature ≥38˚C or ≤ 36˚C
	2. White blood cell count ≥12 000 or ≤4000/mm
	3. Heart rate ≥ 90 beats per minute
	4. Respiratory rate ≥ 20 breaths per minute or Pa CO2 < 32mmHg
Severe Sepsis	**Sepsis with 1 organ dysfunction**
	1. Arterial hypoxemia (PaO2 / FiO2 < 300 Acute Lung Injury) (PaO2/ FiO2 < 250 Acute Respiratory Distress Syndrome in the absent of pneumonia) or (PaO2 / FiO2 < 200 in Acute Respiratory Distress Syndrome the present of pneumonia)
	2. Acute Oliguria (urine output < 0.5 ml/Kg hr or 45mmol/L for at least 2hour)
	3. Creatinine increase (0.5 mg/dL or 44.2 mol/L from baseline)
	4. Coagulopathy (INR > 1.5 or aPTT > 60secs)
	5. Ileus (absent of bowel sound)
	6. Thrombocytopenia (< 100, 000 /L)
	7. Hyperbilirubinemia (> 4mg/dL or 70 µmol/L)
	8. Serum Lactate (> upper limit of laboratory results)
Septic shock	Evident of sepsis with Systolic blood pressure ≤ 90 mmHg after at least 500 – 1000 mL of crystalloids (or 300 – 500 mL of colloids) fluid challenge given over a 30-minute period
Sepsis induced hypoperfusion	1. Septic shock
	2. Lactate ≥ 4mmol
	3. Oliguria

using Early Goal Directed Therapy (EGDT). After 28 days, a follow-up report was conducted via email, through case notes, or telephone call. Following that, patients were sort into two categories which are non-survivor or survivor as an outcome.

STUDY SIZE

Power and sample size was calculated using Open Epi Version 3 based on Fleiss Statistic Method of Rate and Proportion. Calculation of sample size was based on preliminary serum lactate result of our local study, which the sensitivity is 75% and specificity is 77%. For two-sided significant level, the percentage of general population included = 95%. Power of the study = 80%. Odds ratio, the possibility to get disease if being exposed as compare to normal people = 4.9. Ratio of sample size exposed or unexposed = 1. Using Open Epi Version 3, by Fleiss Statistic Method of Rate and Proportion, we estimated that a minimum of 144 total cases would be necessary.

STATISTICAL METHOD

Statistical analyses were performed using SPSS version 20.0. The mean ±standard deviation represents quantitative variables while number and percentage represent qualitative data. Kolmogorov-Smirnov test was used to test normal distribution of data. Fisher's exact test was used in categorical variables while Mann-Whitney U was used in continuous variables test for comparison of survivors and non-survivors. All tests used were two-sided, and statistical significance was determined with $p<0.05$. Receiver-operating characteristics (ROC) curves and area under the curve (AUC) were computed.

RESULTS

CHARACTERISTIC OF STUDY COHORT

From March to April 2014, a total of 375 patients admitted to Emergency Department were suspected with sepsis syndrome. From this amount, 40 patients were eligible and recruited for this study. Twenty one patients were excluded (15 not consented, 6 incomplete data collection). Total of 19 patients data were analyzed. Demographic data are provided in Table 2.

STATIC LACTATE AND LACTATE CLEARANCE

The overall mortality for both group were 25% in lactate non clearance group versus 75% in lactate clearance group. The median static lactate for survivor and the non-survivor at H0, H1 and H6 are showed in Table 3. The results for lactate clearance percentage for both groups at H0-H1, H1-H6 and H0-H6 are showed in Table 4. We found that the threshold for static lactate level to predict 28-day mortality in sepsis for H0, H1 and H6 were 3.9mmol/L, 1.9mmol/L and 2.3mmol/L respectively (Table 5). The ROC curves for that lactate clearance are showed in Table 5.

Table 2: Demographic Data of Study Subject (N=19)

	Overall population (N=19)	Survivors (N=15)	Non survivors (N=4)
Age (year), mean (±S.D)	53.89 (±23.11)	47.87 (±21.38)	76.50 (±14.38)
Gender (%)			
Male	10(52.63)	9 (47.37)	1 (5.26)
Female	9(47.37)	6 (31.58)	3 (15.79)
Race, n (%)			
Malay	11(57.89)	9 (47.37)	2 (10.53)
Chinese	7 (36.84)	5 (26.32)	2 (10.53)
Indian	1 (5.26)	1 (5.26)	0 (0.00)
Sepsis Origin (%)			
Pulmonary	4 (21.05)	3 (15.79)	1 (5.26)
Digestive	5 (26.32)	3 (15.79)	2 (10.53)
Urinary	3 (15.79)	3(15.79)	0 (0.00)
Nervous system	1 (5.26)	0 (0.00)	1 (5.26)
Other	6 (31.58)	6(31.58)	0 (0.00)
Organ Failure, n (%)			
Renal (Creatinine)	1 (5.30)	1 (5.26)	0 (0.00)
Coagulopathy	1 (5.30)	1 (5.26)	0 (0.00)
Serum Lactate	3 (15.79)	1 (5.26)	2 (10.53)
None	16 (84.21)	15 (78.95)	2 (10.53)
Severity of Sepsis, n (%)			
Sepsis	13 (68.4%)	12 (63.16)	1 (5.26)
Severe Sepsis	4 (21.1%)	1 (5.26)	3 (15.79)
Septic shock	2 (10.5%)	2 (10.53)	0 (0.00)
Mortality		15 (78.95%)	4 (21.05%)

Table 3: Static lactate between survival and deceased, median (IQR)

	Survivor (n=15) Median, mmol/L (IQR)	Non survivors (n=4) Median, mmol/L (IQR)	P value
SL H0	1.9(1.2-3.3)	5.3 (3.1-16.0)	0.03 *
SL H1	1.4 (1.2-1.7)	3.9 (2.5-14.8)	0.01 *
SL H6	1.3 (1.0-2.0)	3.2 (2.5-4.0)	0.01 *

IQR interquartile range; *SL* static lactate; *H0* blood lactate at 0 hour*; H1* blood lactate at 1 hour*; H6* blood lactate at 6 hour *statistically significant ($p<0.05$)

DISCUSSION

STATIC LACTATE

All static lactate threshold level was significantly lower in the survivor group from the non-survivor at H0, H1 and H6. The median static lactate for survivor is significantly lower than the non-survivor at H0, H1 and H6 ($p<0.05$) (Table 3). Based on ROC curves, the AUR for at H0, H1 and H6

Table 4: Lactate clearance between survival and deceased, median (IQR)

		Survivors (n=15)	Non survivors (n=4)	P value
LC H0-H1	Median, mmol/L (IQR)	0.5 (0.1-1.4)	1.2 (0.5-1.5)	0.40
	Percentage Clearance %, (IQR)	30% (5.6-41.5)	19% (6.9-27.1)	0.42
LC H1-H6	Median, mmol/L (IQR)	0.3 (-0.5-0.6)	0.7 (0.0-10.9)	0.21
	Percentage Clearance %, (IQR)	15% (-41.2-27.3)	17% (-1.2-64.0)	0.58
LC H0-H6	Median, mmol/L (IQR)	0.7 (-0.1-1.5)	2.1 (0.6-12.0)	0.15
	Percentage Clearance %, (IQR)	38% (-10.0-50.0)	39% (14.5-69.7)	0.48

IQR interquartile range; LC Lactate Clearance ; H0-H1 blood lactate at 0 hour-blood lactate at 1 hour; H0-H6 blood lactate at 0 hour-blood lactate at 6 hour; H1-H6 blood lactate at 1 hour-blood lactate at 6 hour

Table 5: The association between static lactate and lactate clearance to predict 28-day all cause mortality rate.

	AUC (CI=95%)	Threshold (mmol /L)	Se. (CI=95%)	Sp. (CI=95%)	PPV (CI=95%)	NPV (CI=95%)	LR (CI=95%)	OR (CI=95%)	P Value
SL H0	0.867 (0.67-1.00)	3.9	86.7% (59.5-97.9)	75.0 (20.3-95.9)	92.9% (66.1-98.8)	60.0% (15.4-93.5)	0.2 (0.0-0.7)	3.5 (0.6-19.2)	0.04
SL H1	0.917 (0.79-1.00)	1.9	80.0% (51.9-95.4)	99.9.% (40.2-100.0)	99.9% (73.4-100.0)	57.1 (18.8-89.6)	0.2 (0.1-0.6)	-	0.01
SL H6	0.908 (0.77-1.00)	2.3	80.0% (51.9-95.4)	99.9% (40.2-100.0)	99.99% (73.4-100.0)	57.1% (18.8-89.6)	0.2 (0.1-0.6)	-	0.01
LC H0-H1	0.633 (0.39-0.88)	25.9	60.0% (32.3-83.6)	75.0% (20.3-95.8)	90.0 (55.5-98.3)	33.3 (7.8-69.9)	0.5 (0.2-1.2)	2.4 (0.4-13.8)	0.25
LC H0-H6	0.383 (0.07-0.70)	36.3	53.3% (26.7-78.7)	50.0% (8.3-91.7)	80.0 (44.4-96.89)	22.2 (3.5-59.9)	0.9 (0.3-2.9)	1.1 (0.4-3.2)	0.67
LC H1-H6	0.400 (0.09-0.71)	11.6	60.0% (32.3-83.6)	50.0% (32.3-83.6)	81.8 (48.2-97.2)	25.0 (3.9-64.9)	0.8 (0.2-2.6)	1.2 (0.4-0.5)	0.57

AUC area under the curve; *Se.* sensitivity; *Sp.* Specificity ; *PPV* positive predictive value; *NPV* negative predictive value; *LR* likelihood ratio; *OR* odd ratio; *CI* Confidence Interval; *SL* Lactate Clearance; *LC* Lactate Clearance ; *H0* blood lactate at 0 hour; *H1* blood lactate at 1 hour; *H6* blood lactate at 6 hour; *H0-H1* blood lactate at 0 hour-blood lactate at 1 hour; *H0-H6* blood lactate at 0 hour-blood lactate at 6 hour; *H1-H6* blood lactate at 1 hour-blood lactate at 6 hour

suggested that static lactate as a good prognostic tool to predict in 28 days mortality for sepsis. The difference of static lactate between survivors and non-survivors suggests that higher static lactate associates with the increment of mortality rate. Initial static lactate level does correlate with mortality rate thus provides a good prognosis for sepsis (3.85 mmol/L).

LACTATE CLEARANCE – A TOOL FOR MONITORING SEPSIS?

In our study, despite there is a lactate reduction trend at H6, lactate clearance showed a weak association in predicting 28-day mortality in sepsis patients which supports similar findings by Marty et al. (2013). The most plausible explanations for lactate clearance are the increased lactate removal, decreased lactate

production, and dilatation effect due to fluid resuscitation (Jones 2011). Many studies showed that the rise of lactate production after initial resuscitation effort could be due to activation of glycolytic pathway triggered by mechanism such as Na+/K+-ATPase rather than the impact of tissue hypoxia (Hernandez et al. 2010, Gutierrez & Wulf 1996, James et al. 1999, Hotchkiss & Karl 1992, O'Brien et al. 1996). It is also suggested that high initial lactate levels had caused irreversible organ damage (Jansen et al. 2009). Thus, aggressive resuscitations are doubtful to reduce the impact of tissue damage caused initial high static lactate. Besides that, lactate is also a delayed indicator of tissue perfusion which the mechanism is yet to be elucidated (Marty et al. 2013). Age is a possible confounder for static lactate predicting 28-day mortality. Further regression analysis should be carried out in the larger sample size to elucidate this trend.

This study supports recommendation by survival sepsis campaign, which suggests the EGDT should be initiated on patients with static lactate more than 4.0 mmol/L (Hernandez et al. 2010). Interestingly, static lactate at H1 has a threshold 1.9 mmol/L, and it appears to be lower compared with H0 and H6. It may have two possible explanations. First, it may reflect the successful of aggressive resuscitation. Secondly, the dilution effect of fluid resuscitation may lower the lactate level. This marked depression of lactate is not preserved throughout the treatment period. This reflected the resuscitation effort may have slowed down after patient was more stable after the achieving a lower static lactate level at H1.

LIMITATION OF STUDY

There were few limitations to be considered in this study. First of all, this study was done in one hospital, this might have influenced the results. Our study may introduce a selection bias that was difficult to account for. We were unable to keep track and take the blood samples on time as the acutely ill patient was highly mobile in ED to different zone from time to time according to their dynamic of the illness during the recruitment. We were also facing difficulty in getting the consent from the acutely ill patient in the absent of the next of kin. We tried to include as many patients as possible who have fulfilled the sepsis criteria to achieve the estimated sample size (n = 144). However, targeted sample size was partially achieved. The accrual time to reach 144 patients was estimated to be 24 months. It is possible that a larger study may result in different conclusion. The age profile cannot be met as demographic data shows non-survivors appeared in older age group. It prevents further modeling to be performed. Information bias is possible because some information may not have been properly recorded.

CONCLUSION

Our data has shown that with limited number of samples, static lactate was found to be useful to determine survival of sepsis patients. In our centre, static lactate remained as a strong dependent predictor for sepsis in hospital death. In

our study, static lactate is suggested to be superior over lactate clearance as a predictor for sepsis in 28 days mortality. However, lactate clearance can be a useful tool to monitor the resuscitation effort.

ACKNOWLEDGEMENT

We thank the doctors, assistance medical officer, nurses, technical and administrative support staff in the Department of Emergency Medicine of Universiti Kebangsaan Malaysia for their assistance in this study.

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