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Correlation Between Acid-base Balance Parameters and Lactate Concentration with the Outcome in Critically Ill Patients with Metabolic Acidosis

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Henderson-Hasselbach equation (the basic calculation for Base Excess/BE and Anion Gap/AG), lactate concentration and Stewart modified equation (Base Defisit/Excess gap (BDE_{gap}) and Strong Ion Gap (SIG)) are the parameters frequently used by clinicians in order to determine the severity of metabolic acidosis in critically ill patients. The state of metabolic acidosis correlates significantly with poor outcome (mortality). Different methods were used to diagnose metabolic acidosis. The aim of this study was to analyze the correlation between acid-base balance parameters (BE, $AG_{observed}$, $AG_{calculated}$, SIG, BDE_{gap}) and lactate concentration with the outcome in critically ill patients with metabolic acidosis. This study is an analytic study with cross-sectional design involving 70 critically ill patients admitted ICU (Intensive Care Unit) of M. Djamil Central Hospital Padang. The study was conducted from January-September, 2016. Blood gas analysis was measured with potentiometric and amperometric method, electrolytes level was measured with ISE (Ion selective electrode) method and albumin level was measured with a colorimetric method (Bromocresol green/BCG). Multi variate analysis with logistic regression was used to determine which acid-base balance parameters strongly correlates with patient outcome based on odd ratio value more than 1 (OR>1). There were 33 male patients (47%) and 37 female patients (53%). Their ages varied in the range 18-81 years-old (SD 46.3±17.9) and mostly post operative (87%). The mortality rate reached the number of 33%. Logistic regression analysis showed the OR value for BE, $AG_{observed}$, $AG_{calculated}$, SIG, BDE_{gap} and lactate were 0.859 (95% CI, 0.692-[illegible]65), 0.628 (95% CI, 0.447-0.881), 1.470 (95% CI, 0.001-1.596), 0.892 (95% CI, 0.486-1.639), 1.785 (95% CI, 1.267-2.514) and 1.01 (95% CI, 0.10-1.96), respectively. All of the acid-base balance parameters and lactate concentration measured were correlated with the outcome of critically ill patients with metabolic acidosis and strong ion gap (SIG) is the best predictor of outcome in these patients.

Key words: $AG_{calculated}$, $AG_{observed}$, metabolic acidosis, SIG, lactate concentration

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INTRODUCTION

A complex acid-base disorder is frequently found in critically ill patients with metabolic acidosis admitted to the ICU[1]. Metabolic acidosis is a marker of poor prognosis in those patients. Therefore, early recognition of metabolic acidosis is crucial so that those patients could be given appropriate therapy thus improving their outcomes[2].

Assessment of acid-base balance disorder could be determined by using two methods, Henderson-Hasselbach equation (conventional method) which frequently used to measure plasma pH by using BE and AG value and Stewart equation (alternative method) which is done by using BDE_{gap} and SIG value[3]. The use different method could lead to differences in interpretation and treatment strategies for the same disorder. Conventional method often does not depict the real metabolic acidosis state and identification of the underlying causes solely relies on anion gap value. On the other hand, Stewart equations as an alternative method is able to assess small changes of ions concentration involved in maintaining acid-base balance in the body unlike the conventional method[2].

Henderson-Hasselbach equation shows the role of carbonate-bicarbonate buffer in acid-base balance disorder with $PaCO_2$ and HCO_3^- as independent variables for pH[4]. This method has its limitation which is the dependency of HCO_3^- concentration on $PaCO_2$ and difficulty of detecting complex acid-base disorder especially in critically ill patients[3,5].

Siggaard-Anderson complemented the Henderson-Hasselbach equation by adding BE calculation. Base excess is the amount of acid or alkali added into 1 L of whole blood in order to restore blood pH to 7.4 at $PaCO_2$ of 40 mmHg[3,6]. However, Base excess calculation only shows the end result of acid-base disorder and fails to reveal the underlying etiology[7].

$AG/AG_{observed}$ calculation was added to the equation in the state of metabolic acidosis. Anion gap is the difference between the number of cations and anions in the serum and it also shows the unmeasured weak anions in plasma which is mostly albumin. Hipo albuminemia could cause falsely decrease AG value, therefore AG value needs to be corrected ($AG_{calculated}$) against patient's albumin level[3]. However, anion gap could not identify the presence of acid-base disorder due to the changes of plasma free water[7].

The alternative method (Stewart equation) stated that H^+ concentration in a solution is determined by the degree of water dissociation into H^+ and OH^-. There are three independent variables that influence water dissociation, which are strong ion difference (SID), $PaCO_2$ and total weak acid (A_{tot})[8]. However, the Stewart method is difficult to implement due to the many variables that needs to be calculated. Therefore, a number of experts tried to simplify this method, resulted in the Fencl-Stewart and Figge-Stewart method[8-10]. The Fencl-Stewart method calculates BDE_{gap} based on the concentration of Na^+, Cl^- and albumin, while the Figge-Stewart method calculates SIG (the difference between SIDapparent/SIDa and SIDeffective/SIDe) which reveals the presence of unmeasured strong ions[8,9].

Lactate is one of the anions of organic acid that causes acidosis. Lactic acidosis allegedly reported as the common cause of metabolic acidosis in the ICU. Blood lactate concentration is proven to be correlated with the outcome of critically ill patients. A number of researches have shown that the increase of lactic acid in blood would increase mortality rate. It has been reported that the increase of lactic acid in critically ill patients correlates with hypoxia and inflammatory process[1,2].

Critically ill patients commonly experienced a complex acid-base disorder. Previous studies have been conducted in order to know the most appropriate parameters to depict acid-base disorder condition and its correlation with patient's outcome within 28 days of hospitalization (acute term survival)[7,11]. Kaplan and Kellum[12] reported that SIG is a better predictor of mortality compared to $AG_{observed}$, $AG_{calculated}$, BE and lactate concentration in critically ill patients. Gunnerson *et al.*[13] also found that lactate concentration and SIG is a better predictor of mortality compared to BE and $AG_{corrected}$ in critically ill patients. In contrast, Rocktaeschel *et al.*[10] found that none of these parameters observed ($AG_{observed}$, $AG_{calculated}$, BDE_{gap}, SIG) could be used as predictor of mortality in these patients.

It is crucial for the clinician to recognize the early presence of metabolic acidosis in critically ill patients so that the appropriate treatment could be given thus reduces mortality rate. A number of parameters have been introduced to evaluate metabolic acidosis state but the best parameter for clinical applications is still debated. Hence, this study was designed to measure parameters of acid base balance (BE, $AG_{observed}$, $AG_{calculated}$, SIG and BDE_{gap}) and blood lactate concentration and its correlation with the outcome of critically ill patients with metabolic acidosis admitted to the ICU of M. Djamil Padang Central Hospital, in order to find the best parameter to evaluate metabolic acidosis state.

MATERIALS AND METHODS

This study is an analytic research with cross sectional design involving 70 critically ill patients. It was conducted at the emergency room (ER) laboratory and the ICU of M. Djamil Padang Central Hospital from January-November, 2016. The study has been approved by the Research Ethic Committee of the Faculty of Medicine, Andalas University. Informed consent to the patient was not performed since the laboratory test and all samples in this research were collected as per the ICU patient's service standard operational procedure (SOP) of the hospital.

The study population was all critically ill patients in ICU (in accordance to The Acute Physiology and Chronic Health Evaluation (APACHE) score) who had their blood gas analysis and clinical chemistry checked in the ER laboratory of Dr. M. Djamil Padang Central Hospital in the first 24 h of treatment. A consecutive sampling was done to collect the samples from population whom met the inclusion (aged >18 years, have blood pH <7.35 and have electrolyte imbalance) and exclusion criteria (those who have respiratory acidosis). Venous and arterial blood was collected from samples to measure all parameters required in this research. The venous blood was collected in vacutainer without anticoagulant and left at room temperature for 1 h to form a clot. The sample was then centrifuged at a speed of 3500 rpm for 15 min to obtain serum as a specimen for examination of electrolyte concentration and albumin level. After that, the arterial blood that was taken inserted to the anticoagulant-rinsed syringe for the examination of blood gases and lactate concentration.

Examination of blood gas analysis, electrolytes and albumin level: Blood gas analysis was performed with blood gas analyzer GEM Premier 3500. Blood acidity (pH), $PaCO_2$ and Ca^{2+} levels was determined by the potensiometric method while lactate concentration was examined with amperometric method[14]. Electrolytes level was measured with an electrolyte analyzer AVL 9180 that uses an ion selective electrode (ISE) technology[15]. Albumin level was measured with a chemical analyzer ABX Pentra 400 that uses bromocresol green (BCG)[16]. After all of the data were obtained, then $AG_{observed}$, $AG_{calculated}$, BDE_{gap} and SIG were calculated.

Statistical analysis: Mean value, standard deviation, median and interquartile range (IQR) were calculated for each of research variables. Independent variables underwent normality tests using Kolmogorov-Smirnov, while the differences in lab values were assessed by unpaired t-test or Mann Whitney test. Multivariate logistic regression[17] was used to determine the correlation between acid-base balance parameter (BE, $AG_{observed}$, $AG_{calculated}$, SIG, BDE_{gap}) and lactate concentration with the outcome in critically ill patients with metabolic acidosis.

RESULTS

There were 70 patients included in this research. Their basic characteristics could be seen in Table 1. The result value of acid-base balance parameters and lactate concentration is depicted in Table 2.

From Table 1, it can be concluded that the majority of research subjects were women (53%) and the main cause of the research subjects being admitted to the ICU was for postoperative care (87%). Most of the subjects were treated ≤7 days (84%). The majority of patients had improvement before being transferred to the wards with a mortality rate of 33%.

Table 1: Characteristics of subject patients

	n (%)	Interval	Mean±(SD)
Age (years)		18-81	46.3±17.9
Sex			
Men	33 (47)		
Women	37 (53)		
Reasons for ICU admission			
Post operative	61 (87)		
Others	9 (13)		
Duration of treatment (days)		1-18	4.1±3.3
≤7 hari	59 (84)		
>7 hari	11 (16)		
Outcome			
Survive	47 (67)		
Death	23 (33)		

SD: Standard deviation

Table 2: Acid-base balance parameters and lactate concentration value

	Range			
Examination	Minimum	Maximum	Mean (SD)	Median (IQR)
Measured variables				
pH	6.9	7.34	7.26 (0.09)	
pCO_2 (mm Hg)	7.0	45.00	36.34 (7.99)	
Na^+ (mmol L^{-1})	121.0	157.00	134.26 (6.46)	
K^+ (mmol L^{-1})	2.0	6.50	4.11 (0.94)	
Cl^- (mmol L^{-1})	95.0	123.00	106.19 (5.52)	
Ca^{2+} (mmol L^{-1})	0.22	1.01	0.62 (0.16)	
Albumin (g dL^{-1})	1.0	4.00	2.47 (0.80)	
Lactate (mmol L^{-1})	0.4	15.00	3.60 (2.49)	
Calculated variables				
HCO_3^- (mmol L^{-1})	3.0	24.80	17.20 (4.61)	
BE (mmol L^{-1})	-29.8	-1.00	-9.38 (5.45)	
$AG_{observed}$ (mmol L^{-1})	5.6	44.40	14.97 (6.82)	
$AG_{calculated}$ (mmol L^{-1})	8.2	47.65		18.5 (7.22)
BDE_{gap} (mmol L^{-1})	-28.33	10.18	0.99 (7.56)	
SIG (mmol L^{-1})	-2.8	36.42		7.86 (6.96)

SD: Standar deviation, IQR: Interquartile range

Table 3: Correlation between BE, $AG_{observed}$, $TrAG_{calculated}$, BDE_{gap}, SIG and lactate concentration with the outcome of subject patients

	Outcome				
	Survive (n = 47)		Death (n = 23)		
Parameters	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	p-value
BE (mmol L^{-1})	-7.46 (3.62)		-13.28 (6.48)		0.001
$AG_{observed}$ (mmol L^{-1})	13.45 (5.88)		18.10 (7.64)		0.014
$TrAG_{calculated}$ (mmol L^{-1})	1.23 (0.12)		1.36 (0.15)		0.001
BDE_{gap} (mmol L^{-1})	2.79 (6.09)		-2.69 (8.97)		0.013
Laktat (mmol L^{-1})	3.03 (1.84)		4.76 (3.20)		0.022
SIG (mmol L^{-1})*		6.44 (4.93)		11.48 (11.91)	0.001

BE: Base excess, AG: Anion gap, TrAG: Titration of anion gap, IQR: Interquartile range, *Using mann whitney test

Table 4: Multi variate analysis of selected parameters in relation to the patient outcome

	Outcome	
Parameters	p-value	OR (CI 95%)
BE (mmol L^{-1})	0.165	0.859 (0.692-1.065)
$AG_{observed}$ (mmol L^{-1})	0.007	0.628 (0.447-0.881)
$TrAG_{calculated}$ (mmol L^{-1})	0.971	1.470 (0.001-1.596)
BDE_{gap} (mmol L^{-1})	0.713	0.892 (0.486-1.639)
SIG (mmol L^{-1})	0.001	1.785 (1.267-2.514)
Lactate (mmol L^{-1})	0.539	1.101 (0.810-1.496)

OR: Odds ratio, CI: Confidence intervals

Bivariate analysis was done to know the correlation between each variable (BE, $AG_{observed}$, $TrAG_{calculated}$, BDE_{gap}, SIG, kadar laktat) with the outcome and the results can be seen in Table 3. All parameters were included in a logistic regression analysis with results shown in Table 4.

DISCUSSION

Died patients had a more negative value of BE compared to live patients, which indicate a more severe metabolic acidosis state. However, the logistic regression analysis result showed that BE is not a good predictor of mortality compared to other parameters as BE only depicts the end result of acid-base balance disorder without revealing the underlying causes of the disorder[7]. The same result also shown in BDE_{gap} value that died patients had a more negative value of BDE_{gap} compared to live patients. This result indicates the patients suffered from metabolic acidosis before they died. However, multi variate analysis shown that BDE_{gap} is still not a good predictor of mortality since this parameter relies only on Na^+, Cl^- concentration and albumin level without considering other strong ions that also play a role in acid-base balance[8].

Died patients had higher value of $AG_{observed}$ and $TrAG_{calculated}$ compared to live patients. This result suggests that the patients had a severe metabolic acidosis due to the presence of other strong ions. However, this parameter also did not consider all strong ions involved in maintaining acid-base balance and fail to identify acid-base balance disorder caused by changes of plasma free water, thus also not a good predictor of mortality[7].

The Median value of SIG in this research was higher in died patients. This result indicates that these patients had a severe metabolic acidosis due to the presence of other strong ions. In multi variate analysis, higher SIG was positively correlated with the outcome (OR: 1.785, 95% confidence intervals (CI): 1.267-2.514). This result suggests that SIG is a good predictor of mortality as this parameter is taking into account nearly all strong ions that affect acid-base balance.

Lactate concentration was also found higher in died patients. However, result from multivariate analysis showed that it is not a good predictor of mortality in critically ill patients with metabolic acidosis as the unmeasured anions in these patients are heterogeneous due to various causes, not solely caused by lactic acid[18].

Metabolic acidosis state, indicated by the negative value of BE and BDE_{gap} and the increase of $AG_{observed}$, $TrAG_{calculated}$, SIG values and lactate concentration, could induce various effects in body homeostasis which ultimately could lead to the death of critically ill patients. This condition could block calcium channel in the cell membrane and release norepinephrine from sympathetic nerve fibers, thus resulting in vasodilatation and the maldistribution of blood flows. In addition, metabolic acidosis state also causes immune system disorder, arrhythmia, decrease in myocardial contractility and cardiac output and reduction in tissues perfusion[19-21].

This study found that SIG is the best predictor of mortality in critically ill patients with metabolic acidosis. In contrast, Cusack *et al.*[22] reported that SIG has no prognostic value in critically ill patients unlike BE, BDE_{gap}, AG and lactate concentration. Another study, Dubin *et al.*[3], who conducted research to all critically ill patients admitted to the ICU of Sanatorio Hospital Argentina, found that neither lactic acid-base balance, SIG, $AG_{calculated}$, nor BE can be a predictor of outcome in these patients.

The contradictive result obtained in this research might be caused by the differences of research subject criteria. While other research included all critically ill patients without considering metabolic acidosis state, this research included all critically ill patients with metabolic acidosis. Moreover, the number and type of ions measured in each research centre was also different thus affecting the formula that isused. This research did not measure sulphates, phosphates, ketones and magnesium as other causes that increase strong ions in human body. Lastly, differences in measurement method and the type of specimen used could also affect the result of ions level[10,21].

CONCLUSION

It is concluded that critically ill patients with metabolic acidosis have shown increased value of lactate concentration, $AG_{observed}$, $AG_{calculated}$, SIG and BDE_{gap} and decreased value of BE and SIG is the most significant predictor of outcome in critically ill patients with metabolic acidosis.

SIGNIFICANCE STATEMENT

This study finds out the correlation between acid-base balance parameters and lactate concentration with the outcome in critically ill patients with metabolic acidosis which could be beneficial for early recognition of metabolic acidosis so that the appropriate therapy could be given thus improving their outcomes.

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