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Original Article

Agreement of simplified Fencl-Stewart with Figge-Stewart method in diagnosing metabolic acidosis in critically ill children

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Abstract

Background The traditional Henderson-Hasselbalch approach has proven to be imprecise in critically ill patients. Stewart's approach can detect metabolic acidosis missed by traditional approach, including acidosis caused by increased unmeasured agreement (UA). The complexity of Stewart's method leads to development of simpler modifications, simplified Fencl-Stewart and Figge-Stewart method. Agreement between both modifications is unknown.

Objective This study aimed to measure the agreement of simplified Fencl-Stewart with Figge-Stewart method in diagnosing metabolic acidosis in critically ill children.

Methods The was performed in Hasan Sadikin General Hospital, Bandung from July to August 2006, involving <14 year-old critically ill children. Blood samples for gas analysis, sodium, potassium, chloride and albumin measurement were taken simultaneously. Test result was analyzed with simplified Fencl-Stewart and Figge-Stewart method and recorded with Excell spreadsheet. PASS was used for interim analysis and DAG_Stat for raw agreement indices and Kappa calculations.

Results Forty-five (31 males, 14 females) children were enrolled. Acid base disturbances based on Stewart's method were identified in 10 subjects with normal base excess and nine with normal bicarbonate. Significant increase of UA was detected in 11 of 45 subjects with simplified Fencl-Stewart method, compared to that of 12 subjects with Figge-Stewart method. Raw agreement indices showed 95.65% and 98.51% agreement for positive and negative result, Kappa was 0.94 (P=0.0000).

Conclusions Excellent agreement is shown between simplified Fencl-Stewart and Figge-Stewart method in diagnosing metabolic acidosis in critically ill children. Increased UA can be assessed with both methods. **[Paediatr Indones 2007;47:144-149]**.

Keywords: simplified Fencl-Stewart, Figge Stewart, metabolic acidosis, critically ill

Our understanding on acid-base balance has shifted recently since the introduction of modern physiochemical method proposed by Stewart.[1-3] Traditional approach according to Henderson-Hasselbalch equation has been proven unable to detect certain acid-base abnormalities in patients with complex metabolic abnormalities, like metabolic acidosis.[3,4] Stewart's quantitative analysis brings new insights in acid base balance. This new method has the ability to detect acid base abnormalities that are not detected by the traditional approach, and to explain the mechanism of acid base abnormality even in patients with complex metabolic disturbances.[5] Recent studies showed that Stewart's analysis was superior in detecting metabolic acidosis in adults and children with critical illness.[4-9] Complex metabolic disturbances were commonly seen in patients with critical illness, such as electrolyte imbalances and hypoalbuminemia. Low level of serum albumin has known to cloud the identification of metabolic acidosis either with base excess or anion gap analysis.[4] Yet patients with critical illness are the

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ones who need the determination whether metabolic acidosis was present or not.[3] However, the requirement of all cations and anions measurement in plasma, including measurement of parameters that are not routinely done or not available in certain laboratories,[2] and computer literacy are the major set backs in the application of Stewart's quantitative analysis in clinical settings.[2,10] Besides, the time consumed in calculation makes the application in clinical settings impractical.[11]

The complexity of Stewart's quantitative analysis led to development of two modification, known as Fencl-Stewart[12,13] and Figge-Stewart modifications.[14] Both modifications have proven to be as effective as the original Stewart's analysis with the objective of determining the presence of unmeasured anions, requires simpler laboratory evaluation, and have been validated in pediatric patients.[7-9] Recently, Fencl-Stewart modification's five equations has been further modified into three simpler equations, known as simplified Fencl-Stewart.[5] However, this method has not been used in pediatric patients, thus study on this method's accuracy in pediatric patients has to be done before applying it in clinical settings, and the agreement of simplified Fencl-Stewart and Figge-Stewart method has never been measured. This study aimed to measure the agreement of simplified Fencl-Stewart with Figge-Stewart method in diagnosing metabolic acidosis in critically ill children.

Methods

This is an analytic observational study[15] involving children with critical illness, with the age of less than 14 years old, performed from July to August 2006. The design was selective prevalence study, as described by Kleinbaum *et al.*[15] Critically ill children who came to pediatric emergency department, admitted to pediatric intensive care unit, or pediatric ward, or children who were consulted to pediatric department in Hasan Sadikin General Hospital were eligible for the study. Critical illness was defined as conditions with failure or impending failure of one or more organs, resulting in increased mortality and possibility of incomplete recovery.[16] These conditions were compatible with triage level 1 and 2 according to the Canadian Pediatric Emergency Department Triage Acuity Scale.[17] Eligible children who needed blood gas analysis were included in this study after a parental consent was obtained.

Arterial blood for gas analysis was obtained through an arterial puncture with proper method[18,19] in femoral or radial artery.[20] If radial artery was chosen, modified Allen's test was performed to ensure adequate collateral vascular.[21] Three mL blood was taken simultaneously for electrolyte (sodium, potassium, and chloride) and albumin measurement in addition to one mL blood sample for gas analysis. Blood samples were taken on admission and sent immediately for analysis. Blood specimens containing gas bubbles, blood clot, or lyses were discarded. Blood gas was analyzed using Radiometer ABL 855, Copenhagen, Denmark. Electrolytes were measured with ion selective electrode (ISE) using AVL 9198 Analyzer. Albumin level was determined by biuret method using Hitachi 912 Automatic Analyzer, Roche, Ibarachi, Japan.

Test results were interpreted with simplified Fencl-Stewart and Figge-Stewart method to identify metabolic acidosis caused by increased unidentified anions. Test result was also given to the patient's physician for interpretation and further treatment. The involvement of patients in this study did not alter the management, and the patients would still receive appropriate treatment as scheduled. These results were analyzed with raw agreement test,[22] followed by Cohen's coefficient of agreement Kappa[23] using DAG_Stat.[24] Sample size was evaluated with interim analysis using alpha spending function.[25,26]

Results

From July to August 2006, fifty two critically ill children were eligible for this study. Most subjects (33 of 45) were recruited in pediatric emergency unit. Seven subjects were excluded because blood specimens were not drawn simultaneously. Subject's characteristics are shown in **Table 1**. The subjects' age ranged from 36 days to 13 years, with median of two years. Thirty-four out of 45 subjects were under five years old. The most common diagnosis were pneumonia (15 patients) and sepsis (six patients). All pneumonia involved children under five years old. Only one patient with DSS included in this study,

Table 1. Subject's characteristics

Characteristics (n=45)	Number
Triage level	
Level 1	28
Level 2	17
Mechanical ventilation	
Ventilated	24
Not ventilated	21
Organ system and pathology	
Respiratory tract	
Pneumonia	15
Asthma bronchiale	3
Central nervous system	
Infection	3
Intracranial hemorrhage	2
Status epileptics	2
Hypoxic ischemic	
Encephalopathy	2
Guillain Barre syndrome	1
Gastrointestinal tract	
Hollow viscus perforation	3
Urinary tract	
Renal failure	2
Hypertensive encephalopathy	1
Systemic	
Sepsis	6
Ketoacidotic diabetes	1
Dengue shock syndrome	1
Cardiovascular system	
Tetralogy of Fallot	1
Cardiac failure	1

admitted with respiratory distress due to pulmonary edema and pleural effusion.

Acid base balance results are described in **Table 2.**

Electrolyte imbalances were found in 41 subjects, the most common disorder was hyperchloremia (33 subjects), followed by hyponatremia (17 subjects), and hypokalemia (13 subjects). Hypoalbuminemia was found in 24 subjects (53%), only three of them were severely malnourished. Based on traditional approach, only 26 subjects had metabolic acidosis, seven subjects were normal, and four subjects had alkalosis. When evaluated with Stewart's quantitative method, all subjects were obviously had decreased SID resulting in metabolic acidosis.

Table 3 shows agreement between simplified Fencl-Stewart and Figge-Stewart method in identifying unmeasured anions. Overall agreement between both tests was 97.78% positive, and negative result agreement were 95.65% and 98.51% respectively. Both tests showed excellent agreement in detecting the presence of unmeasured anions (Cohen's coefficient of agreement 0.94; P=0.000).[29]

Discussion

Most subjects enrolled in this study were children under five years old. The most common diagnosis were pneumonia and sepsis (**Table 1**). All pneumonia cases involved children less than five years old. Other diagnosis such as DSS, ketoacidotic diabetic involved older

Table 2. Results of blood gas analysis and electrolyte levels

Variables	Range (n=45) Lower	Range (n=45) Upper	Mean	Standard Deviation
Measured variables				
pH	6.84	7.51	7.25	0.17
pCO_2 (mmHg)	5.4	82.6	35.06	18.20
BE (mEq/L)	4.3	-28.6	-10.99	7.85
Na^+ (mEq/L)	111	164	135.78	9.68
K^+ (mEq/L)	1.2	7.6	4.30	1.30
Cl^- (mEq/L)	91	135	111.38	8.13
Albumin (g/L)	12	48	33.40	9.36
Calculated variables				
HCO_3^- (mmol/L)	1.2	29.1	15.06	6.76
SID (mEq/L)	7	39.4	28.70	6.34
BE_{Na-Cl} (mEq/L)	-37	-4	-13.6	6.43
BE_{alb} (mEq/L)	-1.5	7.5	2.15	2.34
BE_{ua} (mEq/L)	-14.8	15.15	0.46	7.69
Anion gap (mEq/L)	-0.2	29.5	13.64	6.94
Corrected anion gap (mEq/L)	3.05	31.95	15.29	6.87

HCO_3^- is calculated with van Slyke formula by blood gas analyzer[27]
SID (*strong ion difference*) , normal value 40-42 mEq/L[3]
BE_{Na-Cl}, BE_{alb}, and BE_{ua} are calculated with simplified Fencl-Stewart formula
AG (*anion gap*) , upper normal limit 20 mEq/L.[9,28]
CAG (*corrected anion gap*) is calculated with Figge-Stewart formula

Table 3. Agreement between simplified fencl-stewart and figge-stewart in identifying unmeasured anions

Method		Simplified Fencl-Stewart Approach BE_{ua} >-5 mEq/L	BE_{ua} =-5 mEq/L	Total
Figge-Stewart Approach	UA <5 mEq/L	33	0	33
	UA =5 mEq/L	1	11	12
Total		34	11	45

Overall agreement : 97.78% Cohen's coefficient of agreement Kappa: 0.94
Positive result agreement : 95.65% P:0.0000
Negative result agreement : 98.51%

children. This pathology and age distribution were similar with the pattern in developed countries. Two third of the patients who required admission into intensive care unit were less than five years old. Respiratory illness is responsible for one fourth to one third of all cases admitted to intensive care. This mirrors the presentation of congenital or hereditary disorders, anatomic and physiologic immaturity including poor immunologic responses, rare exposure to pathogens, and less favorable anatomic size.[16]

Most critically ill patients also face the detrimental effects of electrolyte imbalances and acid base disorders that require immediate care. These disturbances are often the main focus of emergency treatment,[30] thus failure in detecting disturbances may cause inappropriate treatment.[31] Electrolyte disturbances were found in 41 of 45 subjects (**Table 2**), each subject had at least one electrolyte abnormality. The three most common electrolyte disturbances were hyperchloremia (33 cases), hyponatremia (17 cases), an hypokalemia (13 cases). All these strong ion disturbances apparently have the potency in lowering SID, especially hyperchloremia, thus disrupting the balance of water dissociation, enabling formation of more H^+, and resulting in decreased pH.[32] SID calculation revealed metabolic acidosis caused by decreased SID in all subjects, including subjects with normal base excess (10 subjects) and normal bicarbonate (nine subjects).

The incidence of hypoalbuminemia in critically ill children in this study was 53%. Recent work by Durward *et al*[8] showed that hypoalbuminemia was found in 56.7% critically ill children, that was higher than adults (30-40%). The mechanism responsible for hypoalbuminemia in critically ill children were albumin synthesis and degradation imbalance, increased leakage from vascular bed, and altered albumin distribution in vascular and tissues. The function of intravascular albumin in critically ill children is not clear, but it might play a different role from normal people. [33]

The simplified Fencl-Stewart method is considered as the most useful tool in evaluating acid-base status in critically ill patients. This method enables the partition of base deficit according to the cause: electrolyte, albumin, or unmeasured anions.[27,34] Partition of base deficit does not only give better picture of metabolic changes, it also gives information of the etiology of metabolic acidosis. This will affect treatment and prognosis of the disease. Patients with acidosis due to increased unmeasured anions clearly do no need sodium bicarbonate administration,[35] while those with hyperchloremic acidosis need sodium bicarbonate[36] to restore normal SID. Failure to diagnose the type and cause of acidosis will lead to inappropriate treatment and medical intervention.[31]

Acidosis with increased base excess is related with increased mortality. Recent studies showed different cause of acidosis carries different rate of mortality. Lactic acidosis has the highest mortality rate (56%).[37] Hyperchloremic acidosis shows better prognosis.[36,37] These differences showed that BE measurement is not enough, and partition of base deficit will provide more useful informations. This simplified version of Fencl-Stewart is as effective as Fencl-Stewart method in a study involving 300 adults in intensive care unit.[5] Unfortunately, this method has never been validated in pediatric patients.

The concept of anion gap was introduced to compliment Boston and Copenhagen diagnostic system for evaluating acid-base balance. Figge improved this formula with correction for albumin, and this formula is known as Figge-Stewart formula. Corrected anion gap may give similar information as partition of base deficit, [34] but it inherited the weakness of the original anion gap because it still includes HCO_3^- in its calculation, while HCO_3^- is known to be influenced by other components than metabolic.[27] This method has been validated in pediatric patients by Durward *et al*[8].

Raw agreement indices and Cohen's coefficient of Kappa showed excellent agreement between simplified Fencl-Stewart and Figge-Stewart method in detecting metabolic acidosis caused by unmeasured anions. High results for positive and negative agreement showed that the agreement was not merely by chance.[22] Thus both methods can be used to determine the presence of unmeasured anions, especially when lactate measurement is not available.

Generally, people are interested in Kappa analysis as a descriptive statistics,[29] but in this study we also calculated the level of significance for interim analysis. Early stop of the study needed lower alpha value than proposed in the study method.[38] We performed interim analysis with alpha spending function after we recruited 45 subjects, and the level of significance allowed us to stop the study early.

Our study has several limitations. The bias in electrolyte measurement was an inevitable limitation in our study. Although the bias was still within acceptable limits, it was relative large in comparison with such a narrow normal value like SID or AG. Thus interpretation of the result must be done cautiously while remembering the potential error. Second, we did not measure lactate level directly, so it was possible that we have other unmeasured anions in our patients. Measuring lactate and testing its agreement with both modifications will be very useful for hospitals without the facility to measure lactate routinely.

This study shows that acid-base status in critically ill children should be evaluated with either simplified Fencl-Stewart or Figge-Stewart method. BE only describes the presence of acid-base disturbances, and normal BE does not rule out any abnormalities. Both modifications of Stewart's quantitative approach describes the magnitude of the disturbances, as well as the etiology and mechanism responsible for the insult. They allow well tailored fluid and electrolyte administration for every patient, and provide information on the prognosis.

We conclude that there is an excellent agreement between simplified Fencl-Stewart and Figge-Stewart method in diagnosing metabolic acidosis caused by unmeasured anions. Either one should be used for acid-base status evaluation in critically ill children.

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