Diabetic Ketoacidosis in Adolescents and Children: A Prospective Study of Blood versus Urine Ketones in Monitoring Therapeutic Response

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ABSTRAK

Latar belakang: *ketoasidosis Diabetes (KAD) adalah komplikasi Diabetes Melitus (DM) yang berpotensi mengakibatkan kematian. Saat ini belum ada studi di Indonesia yang membandingkan pengukuran kadar beta-hidroksibutirat (β-OHB) kapiler dengan asetoasetat pada urin untuk memonitor respon terapi dari DKA pada remaja.* ***Metode:*** *studi prospektif terhadap 37 remaja dan anak dengan diagnosis KAD di Rumah Sakit Dr. Cipto Mangunkusumo selama Juni 2006-Maret 2011 hingga KAD dinyatakan resolusi. Pemeriksaan gula darah sewaktu, β-OHB kapiler, dan keton urin dilakukan setiap jam, sedangkan analisis gas darah dan elektrolit dilakukan setiap empat jam.* ***Hasil:*** *median waktu resolusi KAD adalah 21 (9-52) jam. Saat median resolusi KAD, terdapat korelasi signifikan yang lebih baik antara kadar β-OHB kapiler dibandingkan dengan kadar keton urin terhadap pH (r= -0,52, p= 0,003 vs r= -0,49, p= 0,005) serta terhadap bikarbonat (r= -0,60, p= 0,000 vs r= -0,48, p= 0,007). Kadar β-OHB kapiler seluruhnya menunjukkan hasil negatif saat median resolusi, sedangkan ketonuria masih ditemukan hingga 9 jam paska resolusi.* ***Kesimpulan:*** *kadar keton darah menunjukkan korelasi yang lebih baik terhadap pH dan bikarbonat untuk menentukan respon terapi KAD pada remaja dan anak bila dibandingkan dengan metode keton urin.*

Kata kunci: *betahidroksibutirat kapiler, ketoasidosis diabetes, keton urin, waktu resolusi.*

ABSTRACT

Background: *diabetic ketoacidosis (DKA) is a potentially lethal complication of diabetes mellitus (DM). There is no study in Indonesia that compares the much-preferred capillary beta hydroxybutirate (β-OHB) measurement to urine acetoacetate in monitoring therapeutic response of DKA in adolescents.* ***Methods:*** *a prospective study of 37 adolescents and children with DKA in Cipto Mangunkusumo Hospital was done between June 2006 and March 2011. The patients were followed until the time of DKA resolution. Hourly measurements of random blood glucose, capillary β-OHB concentration, and urine ketones were done, while blood gas analysis and electrolyte were measured every four hours.* ***Results:*** *median time to resolution was 21 (9-52) hours. Compared to urine ketones, capillary β-OHB concentration showed stronger correlation with pH (r= -0.52, p= 0,003 vs r= -0.49, p= 0,005) and bicarbonate level (r=-0.60, p=0.000 vs r= -0.48, p=0.007) during the median time of DKA resolution. All capillary β-OHB measurement yielded negative results at median time of DKA resolution, while urine ketones were still detected up to 9 hours after resolution.* ***Conclusion:*** *blood ketone concentration*

showed a better correlation with pH and bicarbonate level, as a tool to monitor therapeutic response in DKA in adolescent, compared to traditional urine ketones test in adolescents.

Keywords: *capillary betahydroxybutirate, diabetic ketoacidosis, urine ketones, resolution time.*

INTRODUCTION

Diabetic ketoacidosis (DKA) is a potentially lethal complication of diabetes mellitus (DM).[1] Among young patients with type 1 diabetes mellitus (T1DM), DKA is the most common cause of mortality and the risk of developing the condition ranges around 1-10% per patients per year.[2,3] A report from the Endocrinology Taskforce of Indonesian Pediatric Society from May 2009 to March 2011 demonstrated that 591 children and adolescents were living with T1DM across Indonesia. In 2010, Dr. Cipto Mangunkusumo hospital recorded 98 cases of DKA over a four-year period, which resulted in 14 deaths.[4]

The urinary ketone (acetoacetate) measurement is traditionally used in monitoring DKA patients. This examination does not measure the level of betahydroxybutirate (β-OHB) which is the predominant ketone body in DKA.[5] During the course of DKA treatment, there are drastic changes in ratio of acetoacetate to β-OHB from the normal 3:1 ratio to 7:1, until 15:1.[6] Besides prone to subjectivity, the urine sample collection in young population is often difficult, impractical and time consuming.[5,7] There are many factors that lead to high rates of false positive and false negative results in urine ketone examination.[5,8,9]

In respect of successful DKA therapy, the conversions of β-OHB to acetoacetate take place, owing to chains of oxidative reaction in the liver. In turn, the level of acetoacetate and acetone will rise as the β-OHB concentration falls.[10,11] Motivated by the unreliability of urine ketone to assess DKA severity and insulin response, the American Diabetes Association (ADA) recommends the capillary β-OHB measurement in diagnosis and monitoring of DKA.[12]

This study was the first in Indonesia to compare the correlation between capillary β-OHB and ketone urine level to the blood gas analysis (BGA) parameters, as the standard of monitoring DKA therapeutic response.

METHODS

Subjects aged 5-18 years admitted with diagnosis of DKA to Cipto Mangunkusumo Hospital, Jakarta, were recruited consecutively from June 2006 to March 2011. In this study, DKA was defined as clinical findings of random blood glucose (RBG) >200 mg/dL, pH <7.5 or bicarbonate level <15 mEq/L, positive urine ketones (concentration >0.5 mmol/L), and positive capillary β-OHB (concentration >0.5 mmol/L).

Patients with hyperglycemia due to other causes, diagnosed with respiratory acidosis, and whose parents refused to consent were excluded from the study. Those who failed to follow management protocol or died prior to 36 hours after admission were not included in the analysis.

There were 40 episodes of DKA recorded. Two patients were excluded of unwillingness to participate and one patient who died in the first three hours of care was considered as a drop out. We followed 37 DKA cases during the period of study.

Study Protocol

All patients arrived in the intensive or intermediate care were managed according to the standard procedure of DKA management in our hospital. A prospective analytical study was done to all subjects until the time of DKA resolution. Basic data were obtained along with informed written consent from patients' legal guardians.

Random blood glucose, capillary β-OHB concentration, and urine ketones were measured every hour. Capillary β-OHB was measured using Medisense Optium® (Abbott). Required blood sample for the electrochemical strip was 5 µl, and the result was displayed after 30s. This system was accurate for β-OHB levels from 0 to 6 mmol/l and would show high (Hi) value in above 6 mmol/L. The determination of urine ketones, Multistix® (Bayer) was utilized.

Blood gas analysis and electrolytes (sodium, potassium and chloride) were measured every

four hours. We followed the patients until DKA resolutions were established (GCS=15, random blood glucose ≤200mg/dL and HCO_3 ≥15 mEq/L) or during the first 36 hours since the start of observation.

This study protocol was approved by the Ethics Committee of Faculty of Medicine, University of Indonesia - Cipto Mangunkusumo Hospital, Jakarta.

Statistical Analyses

Data were statistically analyzed using SPSS 17.0 software. Prior to the statistical analyses, data sets were tested for normality, to determine whether statistical correlations were appropriate.

RESULTS

Clinical and Metabolic Characteristics of Subjects

The clinical and metabolic baseline characteristics of the patients are summarized in **Table 1**. Among 37 DKA cases (2 males, 35 females), the average age was 11.7 (SD 2.81). Most subjects were adolescents aged ≥10 years, whose proportion compared to children <10 years old was 30 to 7 (4.28:1). All patients were previously diagnosed with T1DM. The median time to resolution was 21 (9-52) hours. The data distributions of DKA resolution time were abnormal, comprised of <21 hours (24/37), 22-36 hours (4/37), 37-48 hours (8/37), and >48 hours (1/37).

Marked prior laboratory findings in this study (**Table 1**) included the presence of hyperglycemia (473.9 (SD 126.1 mg/dL)), hyperketonemia (4 (SD 1.1 mmol/L)), and urine ketones (median: 8 [4-6] mmol/L). Metabolic acidosis observed with mean blood pH 7.1 (SD 0.1); base excess of -21 (SD 5.2) mmol/L, anion gap of 28.7 (SD 7.1) mEq/dL, and median HCO_3 level of 6.9 (1.8-16.6) mmol/L. The subjects' characteristics are summarized in **Table 1**.

Table 1. Clinical and metabolic characteristics of subjects

Variables	Values (N=37)
Sex ratio (male: female)	1 : 17.5
Age (years)	11.7 (2.81)#
Age group ratio (adolescents : children)	4.28 : 1
Time to resolution (hours)	21 (9-52)*
Duration of insulin infusion (hours)	28 (9-60)*
Random blood glucose (mg/dL)	473.9 (126.1)#
β-OHB (mmol/L)	4 (1.1)#
Urine ketones (mmol/L)	8 (4-16)*
Urea (mg/dL)	34 (10-72)*
BUN (mg/dL)	15.8 (4.64-33.4)*
Creatinine (mg/dL)	0.7 (0.4-1.64)*
Osmolality (mosm/kg)	306.9 (281.84-343.59)*
Blood pH	7.1 (0.1)#
PCO_2 (mmHg)	18.5 (5.2)#
PaO_2 (mmHg)	113.6 (33.1)#
SaO_2 (%)	93.2 (7.2)#
BE (mmol/L)	-21.9 (5.2)#
HCO3 (mmol/L)	6.9 (1.8-16.6)*
Sodium (mEq/dL)	136.8 (5.4)#
Potassium (mEq/dL)	4.8 (0.9)#
Chloride (mEq/dL)	101.1 (5.6)#
Anion gap (mEq/dL)	28.7 (7.1)#

* Median (range); # Mean (SD)

Capillary β-OHB and Urinary Ketone Levels

The median distribution of capillary β-OHB and urinary ketone levels decreased with respect to therapeutic response as shown in **Figures 1** and **2**. Following the median resolution time, there were 8 patients with persistent positive urine ketone until 9 hours after resolution, while β-OHB levels in all subjects were already within normal range.

There was no correlation between both capillary β-OHB level and urine ketones level to BGA parameters during early hours of treatment. At the median time of DKA resolution (i.e. in the 21st hour of monitoring), moderate significant correlations between urine ketones level and blood pH (r=0.49, p=0.005), HCO3 (r=-0.48, p=0.007), and anion gap (r=0.57, p=0.001) were found. On the other hand, moderate trends toward significant correlations were also found between capillary β-OHB level and blood pH (r= -0.52 and p=0.003) as well as HCO_3 (r= -0.60, p=0.000). However, capillary β-OHB level correlated weakly to anion gap during resolution (r=0.37, p=0.04). The comparison between correlations of urine ketones and β-OHB level to blood gas analysis parameters is presented in **Table 2**.

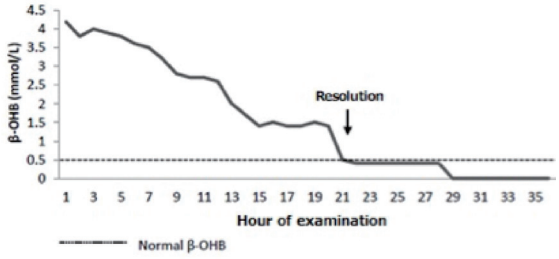

Figure 1. Trend on median value of capillary β-OHB relative to time of measurement.

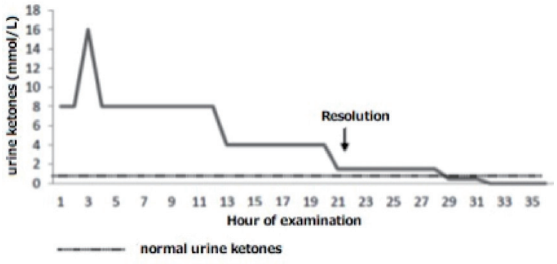

Figure 2. Trend on median value of urine ketones relative to time of measurement.

Table 2. Correlation between urine ketones level and capillary β-OHB level to blood gas analysis parameters

Variables	Correlation coefficient	P value	Correlation formula
pH at the first hour			
- urine ketones	r = -0.14	0.407	
- capillary β-OHB	r = -0.18	0.292	
pH at the 21st hour (median time of DKA resolution)			
- urine ketones	r = -0.49	0.005	pH= 7.38+(-0.01) urine ketones
- capillary β-OHB	r = -0.52	0.003	pH= 7.39+(0.04) β-OHB
HCO3 at the first hour			
- urine ketones	r = -0.04	0.832	
- capillary β-OHB	r = -0.15	0.374	
HCO3 at the 21st hour (median time of DKA resolution)			
- urine ketones	r = -0.48	0.007	HCO3=16.16+(-0.57) urine ketones
- capillary β-OHB	r = -0.60	0.000	HCO3=17.31+(-2.37) β-OHB
Anion gap at the first hour			
- urine ketones	r = 0.15	0.363	
- capillary β-OHB	r = 0.06	0.708	
Anion gap at the 21st hour (median time of DKA resolution)			
- urine ketones	r = 0.57	0.001	AG=11.57+(1.29) urine ketones
- capillary β-OHB	r = 0.37	0.04	AG= 12.82+(2.77) β-OHB

There were moderate significant correlations between capillary β-OHB level and urine ketones at the beginning of monitoring time (r=0.51, p=0.001) and during the median time of DKA resolution (r=0.58, p=0.000), as described in **Table 3**.

Table 3. Correlation between capillary β-OHB level and urine ketones

Blood ketones	Correlation coefficient	Correlation formula for capillary β-OHB and urine ketones
Blood ketones at the first hour	r = 0.51, p=0.001	β-OHB = 3.22 + (2.08) urine ketones
Blood ketones at the 21st hour	r = 0.58, p=0.000	β-OHB = 1.34 + (1.86) urine ketones

DISCUSSION

In this study, we found that DKA episodes were more frequent in female patients, with ratio of 1: 17.5 (male : female). Rewers et al[3] reported no difference in the ratio of DKA incidence between sexes. The difference in this particular study might be attributed to higher number of female patients with recurrent DKA episodes, in accordance to a previous study stating that recurrent DKA affects more female than male population.[13]

Most patients were in the adolescent age category (≥10-year-old). Similarly, a prior study mentioned that the risk of DKA increased in age

5 to 9 years and 10 to 14 years.[3] Higher insulin requirement in early pubertal age is explained by the increasing activities of sex steroids hormones and growth hormones, which both have anti-insulin effects.[14]

The median time of DKA resolution in this study was 21 hours (9-52). DKA resolved in abnormal distributions, with less than 21 hours (24/37), 22 - 36 hours (4 /37), 37-48 hours (8/37), and >48 hours (1/37). One subject, which DKA was resolved in more than 48 hours had infection and cerebral edema.

According to Umpierrez et al[15], the mean time to resolution was 16 (SD 2) hours. Mrozik et al[16] presented DKA resolution with the median time to resolution based on BGA parameters (defined as the median time to reach pH>7.3) at 14.2 (8.6-20.1) hours, HCO_3 >15 mmol/L at 12.9 (8.6-20) hours and anion gap <16.1 at 10.7 (8.2-15) hours. The study observed delayed improvement of acidosis in 50% of subjects related to hyperchloremic acidosis, related to loss of bicarbonate or due to iatrogenic effects of NaCl infusion.[16] Another report of hyperchloremia incidence (indicated by the ratio of plasma chloride to natrium of more than 0.79) increased from 6% to 94%, from early to 20 hours after treatment initiation, respectively. The occurrence of hyperchloremic acidosis might influence the time of DKA resolution. However, the correlation was not tested in this study. To minimize the incidence of hyperchloremic acidosis, a careful calculation in regards to the amount of resuscitation fluid was applied according to the ISPAD consensus.

During the initial period of monitoring, there was no correlation between both capillary β-OHB level and urine ketone to BGA parameters. This finding is consistent with prior studies held by Vanelli et al[7] and Tantiwong et al.[10] Studies regarding correlation between β-OHB and BGA parameters at the time of diagnosis yielded different outcomes. Ham et al[18] showed a significant correlation between β-OHB and pH (r= -0.62, p<0.0001). Similarly, Naunheim[19] found a significant correlation between β-OHB level and anion gap (r= 0.66, p<0.001), while Ali et al[20] stated that β-OHB was significantly correlated with HCO_3 level (r= 0.68, p<0.001).

Later in the course of our study, around the median time of DKA resolution, significant correlations were observed. The correlation of β-OHB to pH is stronger than correlation between urine ketones and pH (r=-0.52, p=0.003 vs. r=-0.49, p=0.04). The correlation between β-OHB and HCO_3 was also stronger compared to the correlation between urine ketones and HCO_3 (r=-0.60, p=0.000 vs. r=-0.48, p=0.007). Conversely, better correlation between urine ketones and anion gap was demonstrated in comparison with β-OHB and anion gap (r=0.57, p=0.001 vs. r=0.37, p=0.04).

Strong correlations between β-OHB level and pH following therapeutic response were reported by Turan et al[21] (r=-0.41, p<0.05), Ham et al[19] (r=-0.61, p<0.0001), Vanelli et al[7] (r=-0.82, p<0.001), and Rewers et al[2] (r=-0.63, p<0.0001). Significant correlation between β-OHB and HCO_3 were also reported by Turan et al[21] (r= -0.35, p<0.05), Vanelli et al[7] (r= -0.63, p=0.001), and Rewers et al[13] (r= -0.74, p<0.0001). Positive correlation between capillary β-OHB level and anion gap was reported by Naunheim et al[19] (r=0.66, p<0.001).

The assessments of metabolic parameters that belong to independent variables in the change of acid-base balance such as lactate, serum albumin, and electrolytes such as calcium, magnesium, and phosphate were not done.[22] The pH and bicarbonate were dependent variables in Stewart's acid-base balance approach, and highly influenced by the many independent variables.[23] Both β-OHB and ketone urine showed lack of correlations to pH, proving that pH was not specific to DKA. Shift in anion gap are correlated with immeasurable cations, protein, and phosphate. Increase in organic acid is also inconsistent with the rise in anion gap. 71% patients with elevated lactate concentration had normal anion gap. This makes anion gap neither sensitive nor specific to acidosis.[24] Despite the low the sensitivities and specificities, the selection of pH, bicarbonate and anion gap as determinants in our study was based on standard criteria released by International Society for Pediatric and Adolescent Diabetes Clinical Practice (ISPAD).[2]

We observed a significant correlations

between β-OHB level and urine ketones in early monitoring period (r= 0.51, p= 0.001) and at the median time of DKA resolution (r= 0.58, p=0,000). A positive correlation between β-OHB level and urine ketones later in monitoring was previously seen 7.8 (SD 2) hours post-therapy; r=0.8, p<0.05), but not in few first hours (3.3 (SD 1.4) hours post-therapy).[21] Prior studies found positive correlations between β-OHB level and urine ketones only at low level.[5,25]

Significant correlation between β-OHB and urine ketone throughout this study showed that β-OHB is equal, if not better, in monitoring DKA therapy response. Periodic examination of capillary β-OHB level was superior compared to urine ketone. Negative capillary β-OHB level (≤0.5 mmol/L) was found in all research subjects by the time of resolution, while 8 subjects remained urinary ketone-positive until 9 hours post DKA resolution. This result is aligned with studies conducted by Umpierrez et al[15] and Guerci et al[11]. Positive urine ketone after resolution of DKA caused by conversion of β-OHB to acetoacetate and the increased hepatocyte oxidative reaction resulted in rise of urinary ketones and acetone levels, along with diminution of capillary β-OHB concentration. The urine ketone test may depict a false picture of ketosis, leading to administration of unrequired high dose of insulin that might be harmful for the patients.[7]

CONCLUSION

Capillary β-OHB elucidated better correlation to pH and bicarbonate when compared to urine ketones upon DKA resolution. A significant correlation between capillary β-OHB and urine ketones suggests that the measurement of blood ketone level may be a replacement for urine ketones examination in monitoring therapeutic response of DKA in children and adolescents.

ACKNOWLEDGMENTS

We would like to thank all personnel of Emergency Room and Pediatric Intensive Care Unit (PICU) of Dr. Cipto Mangunkusumo Hospital, our pediatric residents, and the Endocrinology Division, Departement of Child Health, Faculty of Medicine, University of Indonesia for their contribution throughout the conduct of this study. This study was financed by PT Abbott Indonesia.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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