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Original Article

Association between hyperglycemia and organ dysfunction in shock patients

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Abstract

Background Hyperglycemia is an important marker of both poor clinical outcomes and high mortality rate in critically ill patients. Glucose toxicity results in cell damage that leads to organ dysfunction.

Objective To evaluate for an association between hyperglycemia and the incidence of organ dysfunction in shock patients.

Methods This cross-sectional study was conducted in the pediatric intensive care unit (PICU) of Dr. Moh. Hoesin Hospital, Palembang from June to November 2011. Subjects were consecutively-enrolled, shock patients without a history of diabetes mellitus. Illness severity and organ dysfunction were determined by pediatric risk of mortality (PRISM) III score and pediatric logistic organ dysfunction (PELOD) scores, respectively. Hyperglycemia was defined as a blood glucose level ≥ 110 mg/dL. Statistical analysis was performed with SPSS version 15.

Results Mean age of subjects was 2.30 (SD 2.93) years. Mean PRISM III score was 15.11 (SD 5.63). Prevalence of hyperglycemia was 80.0%. Mean glucose level was 179.51 (SD 86.84) mg/dL. Mean PELOD score was 16.02 (SD 13.87). Organ dysfunction was observed in 86.7% of subjects. The most common organ dysfunction observed in our subjects was liver dysfunction (73.3%). There was a significant association between hyperglycemia and organ dysfunction (OR 43.750; 95%CI 4.036 to 474.252, P=0.001). The blood glucose level cutoff points indicative of organ dysfunction, PRISM III score ≥ 8, and PELOD score ≥ 20.5 were 114.5 mg/dL, 129 mg/dL, and 166 mg/dL, respectively.

Conclusion There is an association between hyperglycemia and organ dysfunction. The upper limit blood glucose level indicative of organ dysfunction is 114.5 mg/dL. A glucose level of 129 mg/dL may be considered to be a warning to start blood glucose monitoring. A level above 166 mg/dL may be used to indicate the necessity of starting insulin therapy intervention. **[Paediatr Indones. 2013;53:26-31.]**

Keywords: *hyperglycemia, shock, organ dysfunction, PRISM III score, PELOD score*

Hyperglycemia is often found in critically ill patients in intensive care units (ICUs). Patients with critical illness, such as shock, may suffer glucose homeostasis disorders and an excess of counterregulatory hormones, such as glucagon, epinephrine, norepinephrine, and cortisol resulting in hyperglycemia. This hyperglycemic condition may interfere with various body systems causing neurological and cardiovasular disorders, as well as fluid and electrolyte imbalance. Furthermore, hyperglycemia may have effects on the immune system, nutrition, and blood coagulation. Cellular interference has been predicted to play an important role in glucose toxicity during acute stress. Glucose toxicity may cause cell damage and organ dysfunction, leading to increased morbidity and mortality rates.[1-4] Currently, there have been few studies on the association between hyperglycemia and the incidence of organ dysfunction in children. In addition, no consensus has been reached by experts on the blood glucose cut-off level that requires intervention.

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We aimed to evaluate for an association between hyperglycemia and the incidence of organ dysfunction in pediatric shock patients.

Methods

This cross-sectional study was conducted from June to November 2011 in the PICU of Dr. Moh. Hoesin Hospital in Palembang. Subjects were shock patients admitted to the PICU and enrolled consecutively. We included shock patients with no history of diabetes mellitus and whose parents provided written informed consent. Shock patients with a history of diabetes mellitus and patients who could not undergo complete laboratory examinations in accordance with the PRISM III and PELOD protocols for any reason were excluded.

There were 45 children who fulfilled the inclusion criteria. We recorded baseline characteristics and collected physical data including blood pressure, temperature, level of consciousness, heart rate, and pupil reflex. Laboratory examinations included blood gas analyses, glucose, creatinine, urea levels, prothrombin time/partial thromboplastin time (PT/PTT), leucocytes and platelets. We assessed illness severity by PRISM III scores, stage of shock and type of shock. A PRISM III score ≥ 8 indicated a high mortality risk. Examinations of blood glucose levels were done every hour during the first 6 hours following PICU admission, and the highest one was taken for our study. Hyperglycemia was defined as a blood glucose level ≥ 110 mg/dL. Organ dysfunction was determined after 24 hours by PELOD scoring. A PELOD score ≥ 20.5 was considered to be a high mortality predictor. Subjects were considered to have dropped out of the study if they passed away or left the hospital before 24 hours of treatment.

Analysis of the relationship between hyperglycemia and organ dysfunction was done by chi square and Fisher's exact tests. Strength of the relationship was expressed in terms of odds ratio (OR). Results were considered to be statistically significant for P values < 0.05. The receiver operating characteristic (ROC) curve was used to find the cutoff point of glucose level in shock patients with organ dysfunction. Logistic regression test was performed to analyze the relationship between interference variables, and independent variables with the dependent variable. All analyses were performed using SPSS 15.0 software.

Results

Of the 45 subjects in our study, 25 (56%) were males and 20 (44%) were females. Subjects' mean age was 2.30 (SD 2.93) years. The modus of age was < 1 year, in which there were 26 patients (58%). Eighteen subjects (40%) had good nutritional status, while 4 subjects (9%) had malnutrition, and 17 subjects (38%) had poor nutritional status. The most common stage of shock found was compensated shock in 36 subjects (80%), followed by decompensated shock in 5 subjects (11%). Thirty-five subjects (78%) were in hypovolemic shock and 6 subjects (13%) were in septic shock. Characteristics of subjects are shown in **Table 1**.

Subjects' mean PRISM III score was 15.11 (SD 5.63). The modus of PRISM III score ≥ 8 was in 41 subjects (91%). The prevalence of hyperglycemia was 36 subjects (80%). Mean highest glucose level in the

Table 1. Characteristics of subjects

Characteristics	n	(%)
Age		
<1 year	26	(58)
1 – 2 years	5	(11)
3 – 4 years	5	(11)
5 – 6 years	3	(7)
7 – 8 years	2	(4)
9 – 10 years	4	(9)
Gender		
Male	25	(56)
Female	20	(44)
Nutritional status		
Malnutrition	4	(9)
Poor nutrition	17	(38)
Good nutrition	18	(40)
Overweight	2	(4)
Obese	4	(9)
Shock stages		
Compensated	36	(80)
Decompensated	5	(11)
Irreversible	4	(9)
Type of shock		
Hypovolemic	35	(78)
Cardiogenic	4	(9)
Septic	6	(13)
Total	45	(100)

first 6 hours after admission was 179.51 (SD 86.84) mg/dL. Pediatric logistic organ dysfunction scoring was performed 24 hours after admission, and the mean was found to be 16.02 (SD 13.87). The greatest proportion of subjects' PELOD scores was > 20.5 in 24 subjects (**Table 2**).

Table 2. Distribution of PELOD score

PELOD score	Frequency	
	n	(%)
> 20.5	24	(53.3)
≤ 20.5	21	(46.7)

Using PELOD scores, we found that 39 subjects (87%) had organ dysfunction, including 33 subjects (73%) with liver dysfunction. In 12 subjects (27%), four types of organ dysfunction were found. Fisher's exact test revealed a significant association between hyperglycemia and organ dysfunction as shown in **Table 3**.

Table 3. The relationship between hyperglycemia and organ dysfunction

Hyperglycemia	Organ dysfunction				Total	
	Present		Not present			
	n	(%)	n	(%)	n	(%)
Positive	35	(97)	1	(3)	36	(100)
Negative	4	(44)	5	(56)	9	(100)

Fisher's test: OR 43.750; 95%CI 4.036 - 474.252; P=0.001

We determined that the blood glucose level cutoff point to predict organ dysfunction in shock patients was ≥ 114.5 mg/dL. The ROC curve revealed a cutoff level of blood glucose to be ≥ 114.5 mg/dL that was associated with organ dysfunction in shock patients, with sensitivity of 89.7% and specificity of 83.3% (**Figure 1**).

The blood glucose level cutoff point in subjects with ≥ 2 organ dysfunctions was 157 mg/dL, with a sensitivity of 77.4% and a specificity of 75.0%. The blood glucose level cutoff point in subjects with ≥ 3 organ dysfunctions was 166 mg/dL, with a sensitivity of 75.0% and a specificity of 72.7%. The blood glucose level cutoff point in subjects with ≥ 4 organ dysfunctions was 168mg/dL, with a sensitivity of 72.7% and a specificity of 58.8%. The blood glucose level cutoff point in subjects with ≥ 5 with organ dysfunctions was 179.5 mg/dL, with a sensitivity of 80.0% and a specificity of 69.0%. The blood glucose level cutoff point in subjects with ≥ 6 organ dysfunctions was 189.5 mg/dL, with a sensitivity of 75.0% and a specificity of 74.3%.

The blood glucose level cutoff point in subjects with PRISM III score ≥ 8 was 129 mg/dL, with a

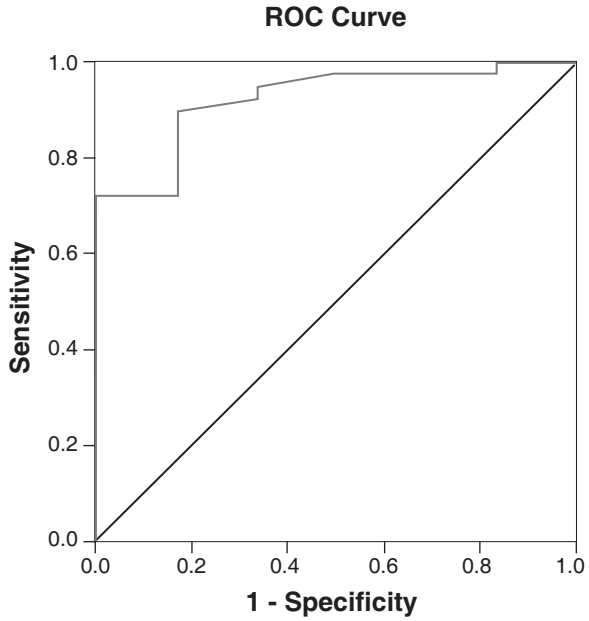

Figure 1. Blood glucose level ROC curve in shock patients with organ dysfunction

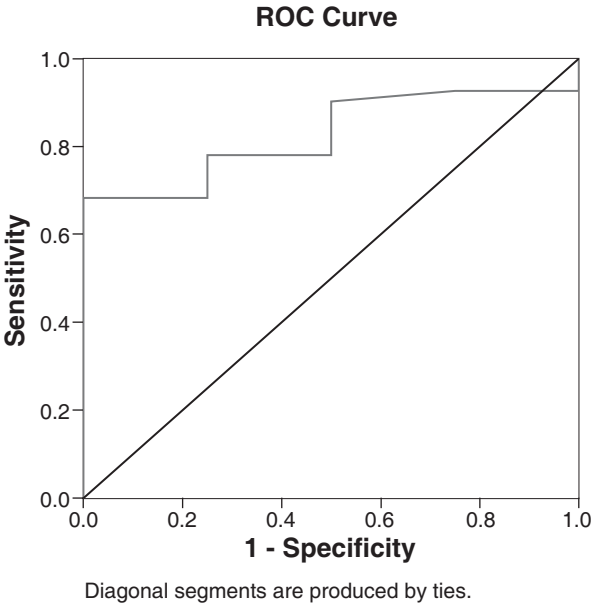

Figure 2. Blood glucose level ROC curve in subjects with PRISM III score ≥ 8

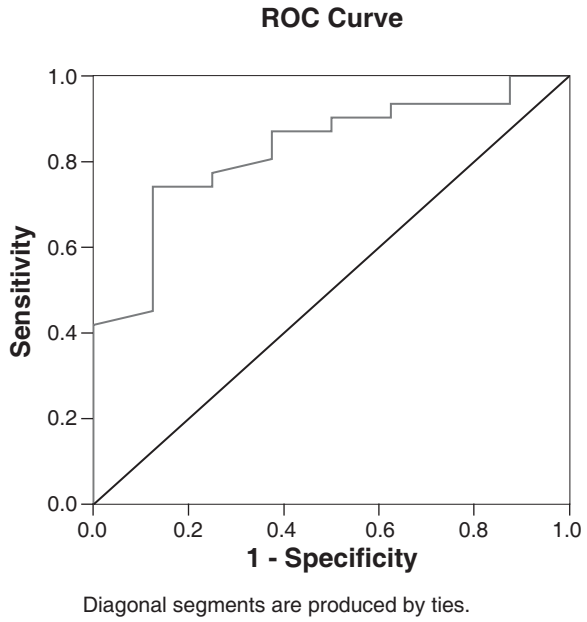

Figure 3. Blood glucose level ROC curve in subjects with PELOD score ≥ 20.5

sensitivity of 78.0% and a specificity of 75.0%. The ROC curve is shown in **Figure 2**.

The blood glucose level cutoff point in subjects with PELOD score ≥ 20.5 was 166 mg /dL, with a sensitivity of 75.0% and a specificity of 71.4%. The ROC curve is shown in **Figure 3**.

Logistic regression test was performed to evaluate the influence of factors that might affect organ dysfunction, such as age, nutritional status, disease severity (PRISM III score), stage of shock, and type of shock. This analysis revealed that the only factor influencing organ dysfunction was blood glucose level (OR 43.750; 95%CI 4.036 to 474.252, P=0.001).

Discussion

Most of our subjects were aged < 1 year (58%). Subjects ranged in age from 1 month to 10 years. The majority of subjects were males (56%). Subjects' characteristics were similar to those in an Indian study which reported that overall prevalence of hyperglycemia in critical illness was 4.7% in 758 children aged between 1 month to 6 years, with a male proportion of 59.5%.[1]

Mean highest blood glucose level during the first 6 hours after admission was 179.51 (SD 86.84) mg/dL. Using a blood glucose level cutoff point of > 110 mg/dL to determine the prevalence of hyperglycemia,[5] we found 36 subjects (80.0%) to be hyperglycemic.

Based on ROC curve, we found that a blood glucose level cutoff point of ≥ 114.5 mg/dL indicated organ dysfunction in shock patients with a sensitivity of 89.7% and specificity of 83.3%. Thirty six subjects were found to have blood glucose levels of ≥ 114.5 mg/dL. Of these, 35 subjects (97%) had organ dysfunction, and 1 subject (3%) had no organ dysfunction. Therefore, blood glucose level of ≥ 114.5 mg/dL was significantly associated with organ dysfunction (OR 43.750; P=0.001). To prevent organ dysfunction in shock patients with hyperglycemia, this data suggests that a blood glucose level of < 114.5 mg/dL should be maintained as a safe upper limit. Cutoff points obtained in our study were similar to a study which reported a prevalence of patients with hyperglycemia and a cutoff point > 110 mg/dL was 86.7%, that of >150mg/dL was 61.0% and that of > 200 mg/dL was 35.2%, which was associated with hospital length of stay (LOS) and mortality. In that retrospective study, subjects were critically ill patients (surgical and non-surgical) with a broad spectrum of primary diseases and a large sample size.[5]

The mean PELOD score of our subjects was 16.02 (SD 13.87). In contrast, Kyle *et al.* reported a mean PELOD score of 19.3 (SD 10.7).[6] This variation may be due differences in the subject population, as well as a much larger number of patients with septic shock. There were 35 hyperglycemic subjects (97.2%) with organ dysfunction and 1 hyperglycemic subject (2.8%) without organ dysfunction in our study. Fisher's exact test revealed a significant association between hyperglycemia and organ dysfunction (OR 43.750; P=0.001). This finding was consistent with a study by Yung *et al.*, who reported an association between hyperglycemia and organ dysfunction (PELOD score ≥ 10; OR 3.41; 95%CI 1.91 to 6.10) and death (OR 3.31; 95%CI 1.26 to 7.7).[7] Also, Srinivasan *et al.* reported that hyperglycemia (>126 mg/dL) in critically ill patients who received mechanical ventilation or vasoactive drugs was associated with a 3.5 times greater risk of death (OR 3.4; 95%CI 1.4 to 8.6).[4] In addition, Branco *et al.* found that there

was a 49.1% increase in mortality rate in pediatric septic shock patients with hyperglycemia, in which blood glucose levels were > 178 mg/dL.[8] Furthermore, Wintergerst *et al*. reported an association between maximal glucose levels, length of stay (LOS), and mortality rate with each value of any cutoff point of hyperglycemia. Patients with blood glucose levels > 110mg/dL had a median value PICU LOS of 4 days and mortality of 5.7%. Those with blood glucose levels > 150 mg/dL had a median LOS of 5 days and mortality of 7.4%. Those with blood glucose levels > 200 mg/dL had a median LOS of 6 days and mortality of 9.9%.[5] In addition, Poddar reported that hyperglycemia > 150 mg/dL was associated with mortality (P=0.004), increased LOS (P<0.0001), and the risk of nosocomial infection (P=0.01).[9]

We observed that higher blood glucose level was associated with more types of organ dysfunction. For ≥ 2 types of organ dysfunction, the blood glucose cutoff point was 157 mg/dL. For ≥ 3 types of organ dysfunction, the blood glucose cutoff point was 166 mg/dL. For ≥ 4 types of organ dysfunction, the blood glucose cutoff point was 168 mg/dL. For ≥ 5 types of organ dysfunction, the blood glucose cutoff point was 179.5 mg/dL. For ≥ 6 types of organ dysfunction, the blood glucose cutoff point was 189.5 mg/dL. The blood glucose cutoff point with PRISM III score ≥ 8 was 129 mg/dL. This value can be used as a warning for the clinician to stringently monitor blood glucose level of patients admited to the PICU with PRISM III score ≥ 8. The blood glucose cutoff point with PELOD score ≥ 20.5 was 166 mg/dL. This value can be used as a consideration for insulin therapy intervention after the first 24 hours or during treatment in the PICU. PELOD scores of ≥ 20.5 have high mortality predictive value.[4]

Several studies have been conducted to determine a safe glucose control target in critically ill PICU patients. A randomized, controlled trial by Van den Berghe *et al*. reported that the administration of intravenous insulin to control glucose levels with a target value of 80-110 mg/dL may reduce the risk of death in intensive care units by 42%. The overall mortality rate in these hospitals was 34%, sepsis rate was 46%, acute kidney failure rate was 41% and tranfusion rate was 50%.[10] Poddar compared intensive insulin administration (glucose target level of 50-80 mg/dL in infants and 70-100 mg/dL in children) with conventional methods of giving insulin to prevent glucose levels higher than 215 mg/dL). They found shorter PICU LOS (P=0.017) and lower mortality in the group receiving the intensive insulin approach (P=0.038).[9]

Organ dysfunction may occur in up to six organs. The largest number of organ dysfunction types in our subjects was four. These results were similar to those of Kyle *et al*. who reported that hyperglycemia was significantly associated with the occurrence of ≥ 3 types of organ dysfunction.[6] We found liver dysfunction to be the most common type of organ dysfunction (33 subjects, 73.3%). In contrast, Ali *et al*. reported renal dysfunction to be the most common type of organ dysfunction.[11] In theory, hyperglycemia leads to impairment of the immune system. The liver plays an important role in the systemic inflammatory response to infection, such as sepsis. In addition, increased transition of pyruvate to superoxide may lead to reactive oxygen species (ROS) due to activation of glycolysis and oxidative phosphorylation. This leads to mitochondrial dysfunction in liver cells. The liver is also a target organ of an ischemic condition that occurs due to various types of shock, since the liver has a high metabolic rate and its function is to break down toxins and other abnormal metabolic factors during shock.[12]

We found that blood glucose level significantly influenced organ dysfunction (P=0.002). Srinivasan *et al*. reported that hyperglycemia increases the electrochemical potential difference caused by the high level of proton in the mitochondrial respiration chain, resulting in longer superoxide transport time and accumulation of ROS. Intracellular ROS will settle and induce cell damage in four stages: increased flow of polyol pathway, increased formation of advanced glycation end products (AGE), activation of protein kinase C (PKC) isoforms, and increased hexosamine levels. Cell damage leads to organ dysfunction, resulting an increased mortality and morbidity.[4]

In conclusion, we find a significant relationship between hyperglycemia and organ dysfunction. The safe glucose level limit that should be maintained to prevent organ dysfunction is 114.5 mg/dL. A glucose level of 129 mg/dL may be used to warn clinicians to stringently monitor glucose levels of PICU patients. A glucose level of 166 mg/dL may be used as a

consideration to start insulin after the first 24 hours or during treatment in the PICU.

A limitation of this study was its small sample size, due to difficulties in obtaining shock patients at the PICU. Also, further study with a broader spectrum of diseases should be conducted to obtain a cutoff point that can be used more broadly in PICU patients with critical illness. The premise of using insulin therapy in patients with PELOD scores of ≥ 20.5 and blood glucose level of 166 mg/dL may be used as a foundation for future studies, because there is not yet a consensus on the blood glucose levels that require insulin therapy in critically ill patients.

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